

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-135**

**CORRESPONDENCE**



Strongin

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 20, 2000

FROM: Supervisory Pharmacologist  
Division of Gastrointestinal and  
Coagulation Drug Products  
HFD-180

SUBJECT: NDA 21,135 (Venofer®/Iron Sucrose Injection) -  
Preclinical Portions of the Labeling

TO: NDA 21,135

The following portions of the sponsor's draft labeling dated July 30, 1999 should be replaced with the accompanying revisions.

1) "PRECAUTIONS"

- a) "Carcinogenesis, Mutagenesis, Impairment of Fertility" -  
Page 9 of sponsor's draft labeling.
- b) "Pregnancy Category B" - Page 10 of sponsor's draft  
labeling.
- c) "Nursing Mothers" - Page 10 of sponsor's draft labeling.

2) "OVERDOSAGE"

- a) "Preclinical Data" - Page 14 of sponsor's draft  
labeling.

Revisions

1) PRECAUTIONS

- a) Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of Venofer®.



Venofer® was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK<sup>+</sup>/-) forward mutation test, the human lymphocyte chromosom aberration test, or the mouse micronucleus test.

Venofer® at i.v. doses up to 15 mg iron/kg/day (about — times the recommended maximum human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance of male and female rats.

b) Pregnancy. Teratogenic Effects. Pregnancy Category B.

Teratology studies have been performed in rats at i.v. doses up to 13 mg iron/kg/day (about 0.5 times the recommended maximum human dose on a body surface area basis) and rabbits at i.v. doses up to 13 mg iron/kg/day (about 1 times the recommended maximum human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to Venofer®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

c) Nursing Mothers:

Venofer® is excreted in milk of rats. It is not known whether it is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Venofer® is administered to nursing women.

2) OVERDOSAGE

Dosages of Venofer® in excess of iron needs -----Infusing the solution as recommended or at slower rate can also alleviate symptoms.

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Single i.v. doses of Venofer® at 150 mg iron/kg in mice (about 3 times the recommended maximum human dose on a body surface area basis) and 100 mg iron/kg in rats (about — times the recommended maximum human dose on a body surface area basis) were lethal. The symptoms of acute toxicity were sedation, hypoactivity, pale eyes, and bleeding in the gastrointestinal tract and lungs.

JS/

- 9/20/80

Jasti B. Choudary, B.V.Sc., Ph.D.

CC:

NDA

HFD-180

HFD-181/CSO, Mr. Strongin

HFD-180/Dr. Choudary

hw/9/20/00

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REQUEST FOR CONSULTATION

49

Division/Office: Peter Cooney, HFD-805  
lawn Building, 18B-08

FROM: HFD-180 (Division of Gastrointestinal and Coagulation  
Drug Products) Brian Strongin

DATE:  
June 20, 2000

IND NO.:

NDA NO.:  
21-135

TYPE OF DOCUMENT:  
BC

DATE OF DOCUMENT:  
June 19, 2000  
16

NAME OF DRUG:  
Venofer (iron sucrose) Injection

PRIORITY CONSIDERATION:  
Standard

CLASSIFICATION OF DRUG:  
Standard

DESIRED COMPLETION DATE:  
September 11, 2000

NAME OF FIRM: Luitpold Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

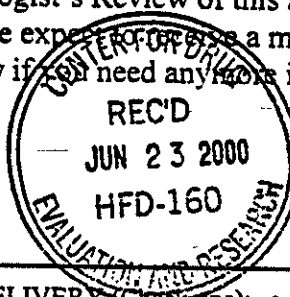
- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY

- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT

- ☐ RESPONSE TO DEFICIENCY LETTER
  - ☐ FINAL PRINTED LABELING
  - ☐ LABELING REVISION
  - ☐ ORIGINAL NEW CORRESPONDENCE
  - ☐ FORMULATIVE REVIEW
  - ☐ OTHER (SPECIFY BELOW):
- See comments below.

COMMENTS/SPECIAL INSTRUCTIONS: Attached is a complete response to our June 8, 2000 CMC information request letter that incorporated the comments/requests from the Microbiologist's Review of this application dated February 24, 2000. The user fee due date is August 6, 2000. However, we expect to receive a major clinical amendment extending the due date until November 6, 2000. Let me know if you need any more information. Thanks.

Original NDA 21-135  
IFD-180/Div. Files  
HFD-180/B.Strongin



SIGNATURE OF REQUESTER:

IS/

6/22/00

METHOD OF DELIVERY (Check one):

☐ MAIL

☒ HAND

SIGNATURE OF RECEIVER:

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SIGNATURE OF DELIVERER:

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MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

Date:            October 27, 2000

From:           Kathy M. Robie-Suh, M.D., Ph.D.    /S/ 10/27/00  
                    Medical Team Leader, Hematology, HFD-180

Subject:        NDA 21-135  
                    Venofer (Iron sucrose injection)

To:              Director, Division of Gastrointestinal and Coagulation Drug Products  
                    (HFD-180)    /S/ 10-27-00

Venofer is an aqueous alkaline solution of ferric ( $\text{Fe}^{3+}$ ) hydroxide complex in sucrose intended for intravenous administration to treat iron deficiency.

Venofer is marketed by Vifor (International) Incorporated in 13 European countries and in about 22 other countries worldwide. The product was first marketed in Switzerland in February 1950. Other names under which the product is marketed include Ferrum Hausmann (Bolivia, Dominican Republic, Ecuador, El Salvador, Guatemala, and Panama) and Ferosac (Saudi Arabia). Indications vary somewhat from country to country but include: for parenteral treatment of iron deficiency in cases where oral iron therapy cannot provide for sufficient supplementation (such as inability to tolerate oral iron, inability to absorb oral iron, or treatment of anemia in dialysis patients with chronic renal insufficiency) or where rapid and reliable repletion of iron is needed (such as, severe iron deficiency or iron deficiency resistant to treatment). The sponsor reports that worldwide ampules of Venofer have been sold since 1986 and about 360,000 patients have received the drug from 1992 and April 1999.

Each 5 ml of Venofer solution for intravenous injection contains 100mg of elemental iron. The structure of the product is described in the package insert for Germany as "polynuclear iron(III) hydroxide cores [which] are superficially surrounded by a large number of non-covalently bound sucrose molecules resulting in an overall complex molecular mass of approximate MW 43kD....The resulting complex is stable and does not release ionic iron under physiologic conditions. The iron in the polynuclear cores is bound in a similar structure as in the case of physiologically occurring ferritin."

In this application the sponsor is seeking approval of Venofer for "treatment of:

- Dialysis-associated anemia



**Dialysis associated anemia:**

For this indication the sponsor has submitted three pivotal studies. Two of these were done in the U.S. (Study LU98001, involving 77 hemodialysis patients treated with Venofer and 60 historical control patients; Study LU98002, involving 23 hemodialysis patients) and one was done in South Africa (Study VIFOR/001, involving 132 hemodialysis patients).

*Study LU9801:* Study LU98001 was a multicenter, open-label, historically-controlled study conducted from December 1998 through July 1999 at 9 U.S. sites. The historical control population was drawn from a natural history of iron deficiency anemia study in 60 hemodialysis patients at a single site at Gambro Health Care Patient Services, Inc. in Tucson, Arizona from April 1998 through time of submission (Van Wyck Study). The study was originally designed to demonstrate efficacy of Venofer by showing achievement of a target blood hemoglobin concentration of at least 11 g/dl in a significant proportion of Venofer-treated patients and showing a significant increase in hemoglobin concentration from baseline for the Venofer treated population. The historical control was incorporated to compare change in blood hemoglobin concentration between Venofer-treated and non-treated patients.

The Venofer-treated patient population consisted of 77 hemodialysis patients aged 24-85 years having hemoglobin concentration greater than 8 and less than 11 g/dl (most with transferrin saturation <20% and serum ferritin <300ng/ml) and who had been on erythropoietin (epoetin, r-HuEPO, Epoetin alfa) (76 for at least 4 months). These patients received Venofer 100mg intravenously up to 3 times weekly for 10 dialysis sessions (1000 mg total dose). Venofer was administered over 5 minutes by injection or infusion pump into the dialysis administration line within 30 minutes after start of the dialysis session. Seventy-four of the patients completed the study (received all Venofer doses and completed both followup visits). The Intent-to-Treat (ITT) population consisted of all patients who received at least one dose of Venofer. An evaluable patient population was also defined consisting of patients who had no major protocol violation, who had received at least 1g of study drug and who had completed end-of treatment evaluation. Demographic features of the ITT and evaluable populations were similar.

The study population from which the historical control population was drawn consisted of 60 adult patients undergoing hemodialysis three times per week, receiving epoetin, not receiving intravenous iron and having hematocrit averaging 31-36 for the 3 months prior to study. Patients were followed for up to 1 year with body iron status and complete blood counts evaluated periodically. Epoetin dose could be gradually increased to double the starting dose to maintain adequate hematocrit; but if adequate hematocrit still could not be maintained, treatment with iron dextran was given and patients were considered to have completed the study. Two patient subsets were defined for analysis with the LU98001 data for efficacy of Venofer: the set of "All Patients" and a "Matched Cohort" for LU98001 (ferritin levels <300 ng/ml at entry).



Demographic and baseline characteristics for the Venofer-treated and historical control patient populations are summarized in the following table:

**Demographic and Baseline Characteristics for Historical and LU98001 Patients**

Parameter	Historical Control		Venofer-treated (LU98001) (N=77)
	All-Patients (N=60)	Matched Cohort (N=24)	
Age (yrs):			
mean	59.9	56.7	62.5
median	62	58.5	64.0
range	27-84	29-80	24-85
Sex, number (%)			
Male	29 (48%)	18 (75%)	44 (57%)
Female	31 (52%)	6 (25%)	33 (43%)
Ethnic Origin, number (%)			
Caucasian	N/A	N/A	36 (47%)
Black			20 (26%)
Asian			5 (6%)
Hispanic			13 (17%)
Other			3 (4%)
Epoetin dose (U)			
mean	3498.3 <sup>a</sup>	3312.5	7942.7 <sup>a</sup>
median	2300	2300	8000
range	1700-10500	1700-10500	500-32000
Ferritin levels (ng/ml)			
mean	418.5 <sup>b</sup>	159.5	146.8
median	406	135	76
range	20-1039	20-291	7-552
Hemoglobin (g/dl)			
mean	11.0	11.1	10.3 <sup>c</sup>
median	11.1	11.2	10.5
range	9.2-12.2	9.9-12.2	7-12
Hematocrit (%)			
mean	35.0	35.2	32.4 <sup>c</sup>
median	35.3	35.7	32.8
range	29.7-41.1	29.7-39.2	23-40
Transferrin saturation (%)			
mean	29.0 <sup>e</sup>	28.1 <sup>d</sup>	16.2 <sup>f</sup>
median	27.0	23.5	14.0
range	16.0-50.0	16.0-50.0	3-48

<sup>a</sup> baseline value for 1 patient missing;

<sup>b</sup> baseline value for 2 patients missing;

<sup>c</sup> baseline values for 37 patients missing;

<sup>d</sup> baseline values for 14 patients missing;

<sup>e</sup> baseline values for 5 patients missing;

<sup>f</sup> baseline values for 36 patients missing.

N/A = not available

based on sponsor's tables

The Venofer-treated patients tended to be slightly older than the matched controls and had higher baseline epoetin doses. Baseline hemoglobin and hematocrit were slightly lower and baseline transferrin saturation was considerably lower for the control patients as compared to the Venofer-treated patients. The epoetin doses in the Venofer-treated patients were generally higher than those in the historical control patients. (FDA Statistical Review conducted ANCOVA on changes from baseline using baseline



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hemoglobin, baseline epoetin dose and baseline ferritin level as covariates). (See FDA Statistical Review and Evaluation by M. Rashid dated 10/17/2000).

The original protocol-specified primary efficacy analysis for Study LU98001 assessing proportion of patients achieving a hemoglobin value of  $\geq 11.0$  g/dl is shown below.

**Table 9 Number and Percent of Patients Who Attained a Hemoglobin Value of  $\geq 11.0$  g/dL: Evaluable and Intent-to-Treat Populations**

Visit	Evaluable Patients			Intent-to-Treat Patients		
	N	%	95% Confidence Interval	N	%	95% Confidence Interval
	45	(100%)		77	(100%)	
Screening (Day -14 to Day 0)	-	-	-	5	(6%)	-
Day 1 (Baseline)	10	(22%)	-	18	(23%)	-
Day 8	16	(36%)	-	28	(36%)	-
Day 15	19	(42%)	-	35	(45%)	-
Day 22	22	(49%)	-	40	(52%)	-
End of Treatment (Day 24)	27	(60%)	[45.3%, 74.7%]	41	(53%)	[41.9%, 64.6%]
2-Week Follow-up (Day 36)	29	(64%)	[50.1%, 78.8%]	47	(61%)	[50.0%, 72.1%]
5-Week Follow-up (Day 57)	33	(73%)	[60.0%, 86.6%]	51	(66%)	[55.5%, 77.0%]
Treatment Effective*	39	(87%)	[76.5%, 96.9%]	60	(78%)	[68.5%, 87.3%]

Extracted from Section 9, Tables 8.1.1 and 8.1.2.

\* Treatment was considered effective if a patient reached the target hemoglobin level at any of the following visits: end of treatment, 2-week follow-up, or 5-week follow-up.

Sponsor's table in NDA Vol. 14.2, pp. 47

About 78% of patients had attained a hemoglobin value of  $\geq 11.0$  g/dl by end-of-study (day 57). However, about 23% of patients had baseline hemoglobin value of  $\geq 11.0$  g/dl. Proportion of patients achieving the target hemoglobin value is displayed below by baseline hemoglobin range for patients who had hemoglobin  $< 11.0$  g/dl at baseline.

**Number of Patients Who Attained a Hemoglobin Level of  $\geq 11.0$  g/dl in ITT Population by Baseline Hemoglobin Level after Excluding Patients with Hemoglobin  $\geq 11.0$  g/dl at Baseline or Screening**

Baseline Hemoglobin (g/dl)	Number of patients	Patients with Hemoglobin $\geq 11.0$ g/dl						
		Treatment				Follow-up		Total*
		Day 8	Day 15	Day 22	End	Day 36	Day 57	
7.3-7.9	3					1	1	2 (66.6%)
8.0-8.9	3						2	2 (66.6%)
9.0-9.4	6			1	1	1	1	4 (66.6%)
9.5-9.9	11		1	2	3	5	5	11 (100%)
10.0-10.4	12	3	5	4	6	8	10	11 (91.6%)
10.5-10.9	15	3	9	10	11	11	12	13 (86.6%)
Total	50	8	15	17	21	26	31	36
	100%	16%	30%	34%	42%	52%	62%	72%

\*including patients who attained hemoglobin level of  $\geq 11.0$  g/dl at either the end of treatment, 2-week or 5-week follow-up visits.

from Medical Officer's Review, p. 36

The majority of patients in both the lower ranges and the higher ranges of baseline hemoglobin level achieved a hemoglobin of  $\geq 11$  g/dl by Day 57 assessment.



It should be noted that there were only two hemoglobin values (screening and baseline) available prior to Venofer treatment. For many patients the amount of increase in the hemoglobin was within the range of variability of the pretreatment value. Therefore, additional validation of the baseline (untreated historical control) comparison was needed.

For the historical control about half of patients started the study with hemoglobin  $\geq 11$  g/dl. In the "all patients" population, at study entry 30 patients (50%) had baseline hemoglobin  $\geq 11.0$  g/dl. During the first 8 weeks (7-9 weeks) of followup values were fairly stable for most patients. About half of patients had a slight decrease or no net change in hemoglobin during this time and almost all of the others had hemoglobin increases of  $< 1$  g/dl. This information is summarized in more detail in the following table.

Directions of Changes in Hemoglobin for Historical Control Patients

	Historical Control			
	All Patients (N=60)		Matched Cohort (N=24)	
	n	%	n	%
Patients with Baseline Hemoglobin $\geq 11$ g/dl	30	50.0%	11	45.8%
Patients with Week 8 (7-9) Hemoglobin $\geq 11$ g/dl	34	56.7	17	70.8%
Patients with Change in Hemoglobin (Week 0-Week 8):				
Decrease	23	38.3%	5	20.8%
Unchanged	7	11.7	4	16.6
Increase $< 1.0$ g/dl	22	36.7	11	45.8
Increase $\geq 1$ g/dl	7	11.7	4	16.6

reviewer's table, based on information in sponsor's 6/30/00 submission.

In the historical control population all the patients having increase in hemoglobin of 1 g/dl or more had either serum ferritin  $> 300$  at baseline and/or large increases in epoetin dose prior to Week 8. Seventeen historical control patients (28.3%) had epoetin dose increased by more than 25% during the first 8 weeks of the study and one additional patient had a smaller increase in epoetin dose; 16 (26.7%) had epoetin decreased and 26 (43.3%) had epoetin dose essentially unchanged over this time. Among the Venofer-treated patients epoetin dose was held constant for most patients. About one-third of patients had a change in epoetin dose during the study: 12 patients (16%) had epoetin dose reduced an average of 39% (range, 8%-90%) of initial dose, 9 (12%) had their epoetin dose increased an average of 43% (range, 25%-122%) and 5 (6%) had epoetin dose both increased and decreased during the study (mean change was a reduction of 1.5%).

Secondary efficacy analyses evaluated change from baseline in hemoglobin, hematocrit and body iron balance parameters. Although two values (screening and baseline) were available for most patients, no prospective plan was described to establish stability of baseline values. Changes from baseline in these parameters are summarized in the following two tables.



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**Table 10 Mean Change From Baseline in Hemoglobin (g/dL): Evaluable and Intent-to-Treat Populations**

Visit	Evaluable Patients (N=45)			Intent-to-Treat Patients (N=77)		
	Baseline <sup>a</sup>	Visit Value	Change From Baseline	Baseline <sup>a</sup>	Visit Value	Change From Baseline
<b>Hemoglobin (g/dL)</b>						
<b>End of Treatment (Day 24)</b>						
N	39	39	39	69	69	69
Mean ± SEM	10.2 ± 0.17	11.5 ± 0.19	1.3 ± 0.17	10.3 ± 0.12	11.3 ± 0.15	1.0 ± 0.12
Median	10.4	11.6	1.3	10.4	11.2	1.0
Min, Max						
95% CI (g/dL)			[0.941, 1.628]			[0.798, 1.292]
<b>2-Week Follow-up (Day 36)</b>						
N	44	44	44	73	73	73
Mean ± SEM	10.2 ± 0.15	11.8 ± 0.18	1.6 ± 0.17	10.3 ± 0.11	11.6 ± 0.15	1.3 ± 0.14
Median	10.4	11.8	1.4	10.4	11.4	1.2
Min, Max						
95% CI (g/dL)			[1.257, 1.957]			[1.018, 1.571]
<b>5-Week Follow-up (Day 57)</b>						
N	42	42	42	71	71	71
Mean ± SEM	10.2 ± 0.16	11.5 ± 0.22	1.3 ± 0.22	10.3 ± 0.11	11.5 ± 0.17	1.2 ± 0.17
Median	10.4	11.7	1.4	10.4	11.7	1.3
Min, Max						
95% CI (g/dL)			[0.877, 1.762]			[0.842, 1.505]

Extracted from Section 9, Tables 8.2.1 and 8.2.2.

CI: Confidence Interval; g/dL: grams/deciliter; SEM: Standard error of the mean; Min: Minimum; Max: Maximum

<sup>a</sup> Baseline was the assessment taken just prior to the start of study drug administration (Day 1).

Sponsor's table in NDA Vol. 14.2, pp. 48

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**BEST POSSIBLE COPY****Table 11 Mean Changes From Baseline in Secondary Efficacy Variables: Evaluable and Intent-to-Treat Populations**

Variable/Visit	Evaluable Patients (N=45)			Intent-to-Treat Patients (N=77)		
	Baseline <sup>a</sup>	Visit Value	Change <sup>b</sup>	Baseline <sup>a</sup>	Visit Value	Change <sup>b</sup>
<b>Hematocrit (%)</b>						
End of Treatment (Day 24)						
N	39	39	39	69	69	69
Mean ± SEM	32.3 ± 0.63	36.0 ± 0.69	3.7 ± 0.49	32.1 ± 0.42	35.2 ± 0.51	3.1 ± 0.37
Min, Max						
95% CI (%)			[2.715, 4.715]			[2.366, 3.842]
2-Week Follow-up (Day 36)						
N	43	43	43	72	72	72
Mean ± SEM	32.4 ± 0.58	37.1 ± 0.65	4.7 ± 0.52	32.4 ± 0.40	36.0 ± 0.53	3.6 ± 0.44
Min, Max						
95% CI (%)			[3.637, 5.722]			[2.757, 4.507]
5-Week Follow-up (Day 57)						
N	41	41	41	70	70	70
Mean ± SEM	32.3 ± 0.61	36.0 ± 0.81	3.7 ± 0.74	32.3 ± 0.41	35.6 ± 0.60	3.3 ± 0.54
Min, Max						
95% CI (%)			[2.185, 5.172]			[2.228, 4.372]
<b>Serum Ferritin (ng/mL)</b>						
End of Treatment (Day 24)						
N	41	41	41	71	71	71
Mean ± SEM	83.6 ± 11.69	360.3 ± 36.81	276.7 ± 30.49	151.7 ± 17.71	456.9 ± 36.21	305.2 ± 25.08
Min, Max						
95% CI (ng/mL)			[215.1, 338.4]			[255.2, 355.3]
2-Week Follow-up (Day 36)						
N	44	44	44	73	73	73
Mean ± SEM	81.4 ± 11.72	264.2 ± 32.71	182.8 ± 26.23	143.3 ± 16.96	357.1 ± 33.92	213.9 ± 22.63
Min, Max						
95% CI (ng/mL)			[129.9, 235.7]			[168.8, 259.0]
5-Week Follow-up (Day 57)						
N	41	41	41	68	68	68
Mean ± SEM	86.5 ± 12.47	223.0 ± 28.49	136.5 ± 22.26	147.1 ± 17.46	302.4 ± 34.13	155.4 ± 25.21
Min, Max						
95% CI (ng/mL)			[91.55, 81.5]			[105.0, 205.7]
<b>TSAT (%)</b>						
End of Treatment (Day 24)						
N	41	41	41	71	71	71
Mean ± SEM	16.9 ± 1.45	25.8 ± 2.05	8.9 ± 1.69	17.6 ± 0.97	26.7 ± 1.57	9.1 ± 1.28
Min, Max						
95% CI (%)			[5.535, 12.36]			[6.581, 11.67]
2-Week Follow-up (Day 36)						
N	44	44	44	73	73	73
Mean ± SEM	17.3 ± 1.41	25.5 ± 1.46	8.2 ± 1.23	17.5 ± 0.98	25.3 ± 1.33	7.8 ± 1.29
Min, Max						
95% CI (%)			[5.723, 10.67]			[5.230, 10.39]
5-Week Follow-up (Day 57)						
N	41	41	41	69	69	69
Mean ± SEM	17.1 ± 1.46	27.6 ± 2.66	10.5 ± 2.41	17.5 ± 1.00	26.2 ± 1.74	8.7 ± 1.65
Min, Max						
95% CI (%)			[5.649, 15.40]			[5.424, 12.02]

Extracted from Section 9, Tables 9.2.1, 9.2.2, 9.3.1, 9.3.2, 9.4.1, 9.4.2.

TSAT: Serum transferrin saturation; CI: Confidence interval; SEM: Standard error of the mean; Min: Minimum; Max: Maximum; %: Percentage; ng/mL: Nanograms/milliliter.

<sup>a</sup> Baseline was the assessment taken just prior to the start of study drug administration (Day 1).<sup>b</sup> Change from baseline.

Sponsor's table in NDA Vol. 14.2, pp. 50

Significant increases in hemoglobin from baseline were seen at end of treatment, 2-week followup and 5-week (Day 57) followup. Similarly, increases were seen in the other



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secondary efficacy parameters. Results for change in hemoglobin and other parameters generally were consistent across age (<65 years and ≥65 years) and sex.

Changes in hemoglobin from baseline for the Venofer-treated (LU98001) patients and the historical controls (Van Wyck) are compared in the following table.

**Table 14. Changes from Baseline in Hemoglobin (g/dL) (Matched Cohort — Van Wyck)**

Visit Window	Treatment	N	Baseline Mean (SE)	Visit Mean (SE)	Change Mean (SE)	95 CI for Change	p-value
Week 4	LU98001	69	10.3 (0.12)	11.3 (0.15)	1.0 (0.12)	0.77, 1.24	0.0004
	Van Wyck	18	11.3 (0.16)	11.3 (0.17)	0.0 (0.21)	-0.41, 0.41	
Week 6	LU98001	73	10.3 (0.11)	11.6 (0.15)	1.3 (0.14)	1.03, 1.57	0.0001
	Van Wyck	18	11.3 (0.15)	10.8 (0.23)	-0.6 (0.24)	-1.07, -0.13	
Week 8	LU98001	71	10.3 (0.11)	11.5 (0.17)	1.2 (0.17)	0.87, 1.53	0.0013
	Van Wyck	15	11.5 (0.16)	11.4 (0.22)	-0.1 (0.23)	-0.55, 0.35	
Endpoint	LU98001	76	10.3 (0.11)	11.4 (0.17)	1.2 (0.16)	0.89, 1.51	0.0001
	Van Wyck	21	11.2 (0.16)	10.8 (0.25)	-0.5 (0.29)	-1.07, 0.07	

p-values: ANCOVA.

Sponsor's table in NDA Vol. 1.20, pp. 39

At all timepoints for patients with assessment available the increase in hemoglobin in the Venofer-treated patients exceeded that in the historical control group. At Week 8 assessment there was a mean increase of 1.2g/dl in the Venofer-treated patients as compared to a mean decrease of 0.1g/dl in the control patients. The differences in mean hemoglobin change remained statistically significant when baseline hemoglobin was added as a covariate in the ANCOVA analysis (p=0.085 at week 4, p=0.0001 at week 6, p=0.0412 at week 8, and p=0.0007 at endpoint). The FDA Statistical reviewer conducted ANCOVA on changes from baseline using baseline hemoglobin, baseline epoetin dose and the baseline ferritin level as covariates. The mean hemoglobin change in the Venofer treated patient group was significantly greater than that in the historical group for all the visit windows (Week 4, p=0.0085; Week 6, p=0.0001; Week 8, p=0.0412). (See FDA Statistical Review and Evaluation by M. Rashid dated 10/17/2000).

Results for changes in secondary efficacy parameters are summarized in the following table.

**Changes in Secondary Efficacy Parameters: Venofer-treated (LU98001) versus Matched Historical Control (Van Wyck)**

Parameter	Treatment	N	Baseline Mean*	Visit Mean	Mean Change	95% CI for Change	p-value
Hematocrit (%): Week 4	LU98001	69	32.1	35.2	3.1	2.36, 3.83	0.0001
	Van Wyck	18	35.8	35.5	-0.3	-1.57, 0.97	
Week 6	LU98001	72	32.4	36.0	3.6	2.74, 4.46	0.0001
	Van Wyck	18	36.0	34.8	-1.2	-2.69, 0.29	
Week 8	LU98001	70	32.3	35.6	3.3	2.24, 4.36	0.0069
	Van Wyck	15	36.3	36.5	0.2	-1.49, 1.89	



Endpoint	LU98001 Van Wyck	75 21	32.3 35.6	35.6 34.8	3.3 -0.8	2.30, 4.30 -2.70, 1.10	0.0003
Ferritin (ng/ml): Endpoint	LU98001 Van Wyck	76 20	146.6 153.9	312.0 126.4	165.3 -27.6	117.8, 212.8 -46.2, -9.0	0.0001
Transferrin saturation (%): Endpoint	LU98001 Van Wyck	76 9	17.6 27.9	26.4 22.8	8.8 -5.1	5.7, 11.9 -13.6, 3.4	0.0016

\* Baseline varies for each visit due to variation in patients with data at visit;  
p-values,

from sponsor's tables

There was statistically significant greater improvement in Venofer-treated as compared to control patients of secondary efficacy parameters consistent with the primary efficacy result.

Results appeared similar across gender, age and race.

*Study LU98002:* This was a multicenter, single arm, open label, baseline controlled study in patients with dialysis-associated anemia who had a previous documented episode of anaphylaxis to iron dextran. The study was carried out at 5 U.S. centers from January 1999 through June 1999. Patients received 5ml of Venofer (100mg elemental iron) intravenously administered either by slow infusion (diluted in 100ml 0.9% NaCl and infused over 15-30 minutes) or by slow injection (undiluted, 20mg/minute injected over 5 minutes). Patients received up to 1000mg of Venofer over 10 dialysis sessions (usually 3 sessions/week).

The study population consisted of 23 hemodialysis patients having history of anaphylactoid reaction/intolerance to iron dextran. Most patients in the study had only mild reaction to iron dextran. Symptoms reported as reaction to iron dextran in these patients are summarized in the following table from the Medical Officer's Review showing symptom events categorized as mild (Group A) or severe (Group B).

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**Symptoms and Signs of Reactions to Iron Dextran in 23 Enrolled Patients**

Symptoms and Signs	Drug	Number of patients
<b>Group A</b>		
Urticaria	Iron Dextran	4
Itchy/back pain/felt hot	"IV Iron preparation"	1
Itchy/felt warm/erythematous	Iron Dextran	1
Itchy/pruritus	Dexferrum	1
Itchy	Dexferrum	1
Nausea/vomiting/upset stomach	Dexferrum	1
Dizziness/hypotension	Iron Dextran	1
Itching/SOB	Dexferrum	1
Chills/itching/rash to head	Iron Dextran	1
Itching and hives	Iron Dextran	1
Stomach cramp/flank pain	Iron Dextran	1
Severe back pain	Dexferrum	1
Rash/hypotension/SOB	Iron Dextran	1
Total		16
<b>Group B</b>		
Coughing/felt hot	Iron Dextran	1
SOB/nausea/chest pain/dizziness	Iron Dextran	1
SOB	Iron Dextran	1
SOB/ chest pain/ weakness/ chills/ back pain/ hypotension	Iron Dextran	1
Asthma/decreased blood pressure	Iron Dextran	1
Collapse	Infed	2
Total		7

Reviewer's table based on the sponsor's data in NDA Vol. 1.29, pp. 26-28.

Among the enrolled patients 4 had screening hemoglobin levels  $\geq 11.0$ g/dl and 5 others had questionable history of allergy/intolerance to iron dextran. Demographic and baseline characteristics for these patients are summarized in the following table:

**Study LU98002: Demographic and Baseline Characteristics for Venofer-treated Patients**

Parameter	Venofer-treated (LU98002) (N=23)
Age (yrs): mean median range	53.0 56.0 21-79
Sex, number (%) Male - Female	10(43.5%) 13 (56.5%)
Ethnic Origin, number (%) Caucasian Black Asian Hispanic Other	8 (35%) 8 (35%) 1 ( 4%) 6 (26%)
Ferritin levels (ng/ml) N mean median	21 50.7 19.0



range	3-230
Hemoglobin (g/dl)	
N	22 <sup>e</sup>
mean	10.38
median	10.5
range	8.5-11.7
Hematocrit (%)	
N	22
mean	32.76
median	33.35
range	26.8-38.4
Transferrin saturation (%)	
N	20
mean	14.87
median	12.3 <sup>f</sup>
range	14.0
	5.0-35.0

from sponsor's table

Generally, the populations in these two studies were similar. The LU98002 patients tended to be younger than patients in LU98001 (mean age 53.0 yrs in LU98002 vs. 62.5 yrs in LU98001) and baseline ferritin levels were somewhat lower in this study than in LU98001 (mean 50.7ng/ml in LU98002 versus 146.8 ng/ml in LU98001). Summary tables for epoetin dose were not provided. However, examination of the patient data listings showed baseline epoetin doses of 2000 U to 17250 U (mean, 8476 U, median 9900 U). Six patients had decreases in their epoetin doses during the study and 3 patients had increases.

Change in hemoglobin from baseline and changes from baseline in the secondary efficacy parameters are summarized in the following table. Twenty-two patients completed study treatment. One patient discontinued study prematurely due to coronary artery disease.

Study LU98002: Mean Change from Baseline to End of Treatment (24 Days)

Parameter	N (n=23)	Mean Change from Baseline	95% CI
Hemoglobin (g/dl)	22	1.14	0.72, 1.57
Hematocrit (%)	22	3.62	2.39, 4.86
serum Ferritin (ng/ml)	21	266.3	203.1, 329.5
Transferrin saturation (%)	20	8.65	4.58, 12.71

CI=confidence interval

from sponsor's table

Overall, there was an increase of about 1.1g/dl in hemoglobin over the 3 to 4 week study period (10 dialysis sessions). Similarly, there were improvements in the secondary efficacy parameters as compared to the baseline values. Results were similar in the two subpopulations (Group A and Group B). Results appeared similar across gender, age and race (Caucasian, Black, Hispanic); there was only 1 Asian patient.

As was the case for LU98001 there were only two hemoglobin values (screening and baseline) available prior to Venofer treatment. And in many cases the change in hemoglobin over the course of the study was within the range of variability of the



untreated value for these patients. Nevertheless, these efficacy results were consistent with the results of Study LU98001.

*Study VIFOR/001 (van Zyl-Smit Study):* This was a multicenter, single arm, open-label, baseline controlled study conducted in South Africa from August 1994 through October 1995 of Venofer (100mg elemental iron 2-3 times per week administered intravenously into the dialysis line) in 131 patients with iron deficiency anemia on chronic hemodialysis. The protocol for this study specified a test dose of 2.5ml (50mg elemental iron) diluted in 50 ml 0.9% NaCl and administered within 3 to 10 minutes at the first dialysis session of the study. At subsequent dialysis session patients received 100mg intravenous Venofer. Cumulative dosing was 1-27 doses (mean of 14.7 doses total; 2-3 dialysis sessions per week).

More patients in this study were Coloured or Black (72%) and patients were younger than in-LU98001 and LU98002 (mean age 41.6 years) and only about 20% of patients were on epoetin treatment. About 20% of patients were excluded from the efficacy analysis, most commonly because of undergoing renal transplant or violations of inclusion criteria.

Change in mean hemoglobin, hematocrit and iron parameters at Week 2 and at end of study are summarized in the following table:

Study VIFOR/001: Mean Changes in Hematology and Iron Parameters

Efficacy Measures	Baseline	Observation Week 2	Post-Study	Change Post-Study
Hemoglobin (g/dl): mean range	7.2	8.8	9.0	1.8
Hematocrit (%): mean range	22.4	27.1	27.7	5.3
Serum ferritin (ng/ml): mean range	74.5	486	450	375.5
Serum transferrin saturation (%): mean range	13.6	25.8	25.7	12.1
Total Iron Binding Capacity (TIBC): mean range	54.9	44.3	43.7	-11.2

based on sponsor's tables NDA Vol. 1.18, pp. 191 and 194

Statistically significant improvement was seen in all these efficacy parameters at both Observation Week 2 and Post-Study ( $p < 0.0001$ , sponsor's analysis of log transformed data). Results appeared similar across gender and race (few Asian patients). There were only 2 patients  $\geq 65$  years of age.

As was the case for the previous two studies, there were only two hemoglobin values (screening and baseline) available prior to Venofer treatment. The change in hemoglobin over the course of the study was within the range of variability of the untreated value for



these patients. Nevertheless, these efficacy results were consistent with the results of Study LU98001.

*Other Studies:* Four additional studies were reported for this indication. For three of these studies, protocols were either not available (Study Al-Momen; Study Yavuz) or incomplete (Study Hussain).

- Study Al-Momen was a non-randomized, open label study which involved 123 patients treated with either Venofer or no iron for 12 weeks. Also, epoetin doses were increased in poorly responding patients. Improvement from baseline was seen for hemoglobin and hematocrit for both groups but serum iron parameters did not improve in the no iron group. (Stability of baseline values was not established). The improvement in all parameters was greater in the Venofer-treated group as compared to no iron treatment group.
- Study Yavuz was a single center, non-randomized, open-label study to investigate use of Venofer with epoetin in 30 hemodialysis patients for 24 weeks. Improvement from baseline was seen for hemoglobin and hematocrit with or without iron. (Stability of baseline values was not established). Serum iron parameters did not improve in the no iron group.
- Study Hussain was an open-label comparison of iron-hydroxide-sucrose complex (VENOFERRUM) versus oral iron for 12 weeks in 20 hemodialysis patients on epoetin. Mean hemoglobin increased in both groups from baseline to final visit with borderline better result for intravenous iron. (Stability of baseline values was not established). Epoetin dose at end of study was higher in oral iron group than in intravenous iron group.
- Study Schaefer was a single center, non-randomized, open-label comparison of Venofer and Ferrlecit in 59 hemodialysis patients. Mean baseline hemoglobin was 11.3. Neither treatment group showed significant improvement by end of study and there were no significant differences between treatment groups.

Comments: Study LU98001 is an adequately controlled study demonstrating a benefit of Venofer 100mg given intravenously during dialysis session in patients with hemodialysis associated anemia in improving blood hemoglobin, hematocrit and iron balance parameters. The improvement from baseline in these parameters is greater in the Venofer-treated patients than in the untreated matched historical control. Studies LU98002 and VIFOR/001 provide additional support for the indication. The other studies submitted though not inconsistent with effectiveness of Venofer were not adequately designed or conducted to provide meaningful support for the indication.

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No studies were submitted specifically to address this claim. A two center, randomized, double-blind study of Venofer alone versus Venofer in combination with epoetin for 16 weeks in 40 Crohn's disease patients with iron deficiency anemia was submitted (Study



50). Both groups showed increase in hemoglobin from baseline to end of study. However, stable baseline values were not established. Study 52 was a single-center, open-label, non-randomized study of intravenous Venofer versus Ferrlecit in 121 patients with malabsorption or oral iron intolerance. Both groups in this study showed significant increase in hemoglobin and improvement in iron balance parameters from baseline to final visit. However, stable baseline values were not established. There was no significant difference in hemoglobin change between treatment groups.

No studies were submitted specifically to address this claim. In the one study (Study LU98002) where enrolled patients were to have history of allergic reaction to iron dextran, the documentation for the allergic reaction was poor for most of the 23 enrolled patients and in many cases reported reactions were very nonspecific (e.g., "itching"). Most reported reactions were mild in severity. During treatment with Venofer, when similar reactions occurred they were not necessarily categorized as allergic in nature.

One open-label study in 20 hemodialysis patients comparing treatment with intravenous Venofer to oral iron (Study Hussain) showed improvement of hemoglobin levels from baseline in both treatment groups. However, stability of hemoglobin at baseline was not established.

#### Safety:

The 3 studies supporting approval of Venofer for use in hemodialysis patients involved a total of 291 patients, 231 of whom were treated with Venofer. Most of these patients received Venofer doses of 100mg at one or more dialysis sessions (up to 1000mg iron total dose). Among the most frequent adverse events were hypotension and muscle cramps. Some of the more common events occurring during Venofer treatment in these three studies are summarized in the following table:

Frequency of Selected Adverse Events during Treatment Period in Venofer Trials in ESRD Patients

Event	Percentage of Patients		
	Study LU98001 (N=77)	Study LU98002 (N=23)	VIFOR (N=131)
Hypotension	17%	44%	44%
Headache	5%	22%	13%
Hypertonia	3%	26%	0%
Musculoskeletal/leg cramps	5%	4%	8%
Injection site reaction	9%	4%	5%
Pain	10%	13%	35%
Abdominal pain	8%	0%	5%
Diarrhea	9%	4%	4%

reviewer's table based on information in sponsor's adverse events tables



In these studies about 4% of patients discontinued Venofer treatment due to adverse events; about 15% experienced serious adverse events and 3 patients (about 1%) died during the observation period. Adverse events leading to withdrawal from study treatments included: graft rejection and/or renal transplant problems (4 patients), gastroenteritis (1 patient), gastrointestinal bleeding, drop in hematocrit, reduced neutrophils and tiredness/sleepiness. Serious adverse events occurring in 2 or more patients included: pneumonia (6 patients), gastrointestinal hemorrhage (4 patients), injection site hemorrhage/reaction (3 patients), infection/sepsis (3 patients), angina pectoris (2 patients), and graft rejection (2 patients). Numbers of patients with discontinuation due to adverse events, serious adverse events, and deaths are summarized in the following table:

**Discontinuations Due to Adverse Events, Serious Adverse Events and Deaths in Venofer Trials in ESRD Patients**

Event	Number of Patients		
	Study LU98001 (N=77)	Study LU98002 (N=23)	VIFOR/001 (N=131)
Discontinuations due to Adverse Events	1	0	8
Serious Adverse Events	14	3	16
Deaths	2 <sup>a</sup>	0	1 <sup>b</sup>

<sup>a</sup> 56 year old black man with cardiomyopathy, congestive heart failure, hypertension, diabetes mellitus with poorly controlled serum glucose levels, chronic renal failure on dialysis, multiple medications found dead at home 2 days after receiving Venofer; events judged unrelated to Venofer.

45 year old black woman with ESRD due to glomerulonephritis and "parathyroid disorder" underwent parathyroidectomy and developed perineal necrosis and disseminated intravascular coagulation; pt died 11 days after surgery and 1 month after last Venofer dose; events judged unrelated to study drug.

<sup>b</sup> 23 year old mixed race woman with chronic renal failure on hemodialysis underwent renal transplant while on Venofer in study, hypochromic anemia worsened and patient had acute graft rejection and was withdrawn from the study; patient apparently died a few days after last Venofer dose; events were judged unrelated to Venofer.

reviewer's table based on information in sponsor's study report

Venofer infrequently showed some evidence of allergic-type reactions during these studies. There were no instances of bronchospasm, laryngoedema or angioedema. However, in Study LU98001 one patient reported mild pruritus (and received Benadryl); in Study LU98002 two patients reported dyspnea, two had some pruritus, and one reported dyspnea; and in VIFOR/001 one patient developed urticaria and another, pruritus. As described above, hypotension was among the more frequent adverse events occurring in these studies. The postmarketing safety database for Venofer also contains cases of anaphylactic/anaphylactoid reactions with Venofer.

**Test dose:** Only one study (VIFOR/001) specified that patients be given a test dose of study drug before administration of the full dose. (The test dose was to be 50 mg Fe(III) (i.e., 1/2 of the full dose) which was to be diluted in 50 ml 0.9% NaCl and administered within 3 to 10 minutes). However, all three protocols instructed that Venofer dose (100mg) was to be given over a period of time ranging from 5 to 30 minutes. Rate of administration was not specified. It is not clear how actual rate of infusion of Venofer was selected for individual patients and whether the infusion rate was adjusted or interrupted once Venofer administration had begun. Because the other available iron



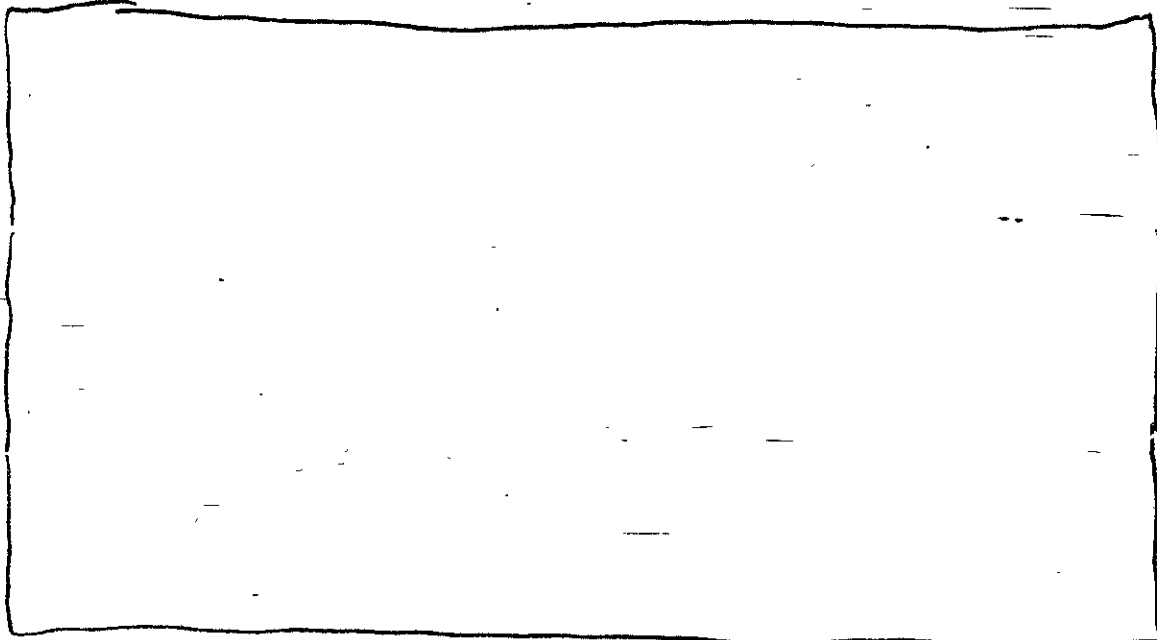
injection products have labeling that recommends a test dose (25mg iron(III)) due to concern about occurrence of anaphylactic/anaphylactoid reactions, it is not unreasonable to assume that some of the patients in these Venofer studies may have received part of at least the first dose as a "test dose" of some sort. Because of the concern about allergic-type reactions, I feel it is prudent to include in the Venofer labeling a recommendation for a test dose similar to that in the Ferrlecit (sodium ferric gluconate complex in sucrose injection) and INFeD (iron dextran injection) labeling.

**Conclusions and Recommendations:**

- Dialysis-associated anemia

The sponsor has provided substantial evidence from adequately (though not optimally) conducted and designed clinical trials to support the use of Venofer in patients with hemodialysis associated anemia.

I concur with the recommendation in the primary Medical Officer Review that Venofer be approved for the indication: treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. The dose should be 100mg elemental iron at 1-3 dialysis sessions per week to a total dose of 1000mg. The dose should be administered either undiluted by slow injection into the dialysis line or diluted in 100ml of 0.9% NaCl and infused over 5-15 minutes into the dialysis line. A test dose should be recommended as in the current INFeD and Ferrlecit labeling. Efficacy information from Studies LU98001, LU98002 and VIFOR/001 should be included in the labeling.





The post-marketing safety database mentions 2 deaths and 3 serious cases of necrotizing enterocolitis in pre-term infants in a French study. Additional efficacy and safety information is needed to support use of Venofer in the pediatric population. The sponsor should do the following:

1. Address use of Venofer in adolescents (ages 12 to 16 years). This can be done, for example, by presenting information and discussion making the case that adolescents are sufficiently similar to adults with regard to disease and beneficial and adverse responses to Venofer so that efficacy data from adult patients may be extrapolated to adolescents. Alternatively, the sponsor may propose a clinical efficacy trial of Venofer in adolescents comparable to the efficacy trials used as primary support for approval of the NDA.
2. Conduct a single-dose pharmacokinetics study of Venofer following intravenous administration to adolescent hemodialysis patients on epoetin.
3. Conduct an adequate and well-controlled clinical trial of safety and efficacy of Venofer in the treatment of iron deficiency in children (aged 2 to 12 years) who are on hemodialysis and receive epoetin. (Use of an active control, such as oral iron, or dose ranging comparison should be considered in designing this study).

1/ST

Kathy M. Robie-Suh, M.D., Ph.D.

10/27/00

cc:

NDA 21-135  
HFD-180/Division File  
HFD-180/BStrongin  
HFD-180/KRobie-Suh  
HFD-180/MLu  
HFD-720/TPermutt  
HFD-180/JChoudary  
HFD-870/SDoddapaneni  
HFD-180/LZhou

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# MEMORANDUM OF 45-DAY PLANNING/FILING MEETING

Date: September 27, 1999

Application Number: NDA 21-135

Drug: Venofer® (iron sucrose injection)

## Attendees:

Dr. Florence Houn	Director	HFD-103
Dr. Lilia Talarico	Director	HFD-180
Dr. Steve Aurecchia	Deputy Director	HFD-180
Dr. Kathy Robie-Suh	Medical Team Leader/Hematology	HFD-180
Dr. Min Lu	Medical Officer	HFD-180
Dr. Liang Zhōu	Team Leader, CMC	HFD-180
Dr. Ray Frankewich	Review Chemist	HFD-180
Dr. Jasti Choudary	Team Leader, Pharm/Tox	HFD-180
Dr. David Joseph	Review Pharmacologist	HFD-180
Dr. Paul Flyer	Team Leader, Biometrics	HFD-715
Dr. Mushifqur Rashid	Mathematical Statistician	HFD-715
Dr. David Udo	Biopharmaceutics Reviewer	HFD-870
Dr. Khairy Malek	Medical Officer	HFD-45

## Background:

NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. dialysis-associated iron deficiency anemia;

Efficacy in dialysis-associated anemia is supported by two pivotal studies. Study VENO/BGSA-VIFOR/001 FARMOVS 52/93 is a multi-center, baseline-controlled study conducted in 132 patients in South Africa (van Zyl-Smit et al, 1997). Study LU98002 is a multicenter study in 23 patients designed primarily to determine whether Venofer® can be safely used in patients with dialysis-associated anemia who had previously demonstrated anaphylactic reactions to iron dextran, although efficacy endpoints were also measured. Efficacy for the remaining indications is supported by 27 publications/study reports (7 controlled, 3 with data tabulations).

## Meeting:

- I. Filing Issues
  - A. Administrative: None

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- B. Clinical: None
- C. Pharmacology: None
- D. Chemistry/Manufacturing/Controls: None
- E. Statistics: None
- F. Microbiology: None
- G. Biopharmaceutics: None

II. Requests for Information

- A. Administrative: Unannotated labeling in WORD 97 on diskette will be requested from the firm.
- B. Clinical: Dr. Lu will review the gender, race, and age subgroup analyses of the safety and efficacy data submitted by the sponsor and ask the Project Manager to request additional information/analyses if necessary.
- C. Chemistry/Manufacturing/Controls: Information requests will be conveyed to the Project Manager and forwarded to the firm as soon as available.
- D. Statistics: Efficacy data from all studies for which data tabulations are available in SAS data set format on diskette will be requested from the firm.
- E. DSI: Recommendations for study sites to audit will be provided from the Medical Officer to the Project Manager and forwarded to DSI.

III. Conclusions

It was decided that the application would be filed. Venofer® will be classified as a new molecular entity (NME) pending the development of a policy statement from the Office of New Drug Chemistry regarding drug classification for injectable iron preparations. A five-month team meeting to discuss the progress of reviews will be scheduled for January, 2000.

Minutes Preparer:           / S /                     9/30/99            
Concurrence:           / S /                     9-30-99          

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## MEMORANDUM OF TELECON

DATE: June 8, 2000

APPLICATION NUMBER: NDA 21-135; Venofer (iron sucrose injection)

BETWEEN:

Luitpold Pharmaceuticals, Inc.

Mary Jane Helenek  
Suzanne Gagnon, M.D.  
Peter S. Reichertz

Senior Vice President  
Vice President of Clinical Research and Development  
Counsel to Luitpold, Arent Fox Kintner Plotkin & Kahn,  
PLLC

AND

The Division of Gastrointestinal and Coagulation Drug Products

Lilia Talarico, M.D.  
Kathy Robie-Suh, M.D., Ph.D.  
Min Lu, M.D.  
Brian Strongin

Director  
Medical Team Leader, Hematology  
Medical Officer  
Regulatory Health Project Manager

SUBJECT: Clinical Comments

Background

NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. Dialysis-associated iron deficiency anemia;

February 1, 2000 the firm submitted a protocol entitled, "An Open Label Study of the Safety of Venofer [Iron Sucrose Injection] When Administered Without a Test Dose" to IND. Comments and recommendations regarding the protocol were sent to the firm in an information request letter dated March 29, 2000. In an April 27, 2000 teleconference with the firm, the Division discussed the comments/recommendations regarding the protocol as well as provided comments regarding the efficacy database for NDA 21-135. (See Medical Officer's



Review dated May 1, 2000, IND ——— for a record of the discussion.) A follow-up teleconference to discuss these issues was held June 6, 2000. The firm requested today's call to further discuss these issues.

### Today's Call

The firm explained that they had requested today's teleconference to ensure that the Division was focusing on the entire clinical database submitted to NDA 21-135, including the supportive studies, rather than only the three pivotal studies (The van-Zyl Smit study, Study LU98001, and Study LU98002). Dr. Robie-Suh responded that, although several clinical studies were submitted, most of the study reports had serious deficiencies including lacking protocols, incomplete or absent data listings, and inadequate adverse event reporting. The firm stated that the study entitled, "Enhancement of rHuEPO Effect By Iron(III)-Hydroxide Sucrose Complex in Hemodialysis Patients" (Volume 1.30, August 6, 1999 submission) may provide additional efficacy support. Dr. Talarico responded that this study could not be considered an adequate and well-controlled study because, among other things, patients were not randomized and there were imbalances between treatment groups.

Drs. Talarico and Robie-Suh explained that, although the clinical database suggested the efficacy of Venofer® for the treatment of dialysis-associated iron deficiency anemia, all studies had serious deficiencies in design and conduct such that they did not provide sufficient evidence as adequate and well-controlled studies. She reminded the firm that approval could not be based on perceptions or prior approval in other countries. The studies did not provide unquestionable evidence of efficacy and allow quantification of the effect of Venofer®. As discussed in the April 27 and June 6, 2000 teleconferences with the firm, the lack of a clearly established, stable baseline in the baseline-controlled studies is the most serious deficiency in the pivotal studies. The firm reminded the Division of the June 9, 1998 pre-NDA meeting and expressed dismay that more specific comments regarding the proposed baseline-controlled studies were not given. Dr. Talarico reiterated the Division's comments from the June 9 meeting that baseline controls are an acceptable type of historical control, and added that a stable baseline must be validated.

Dr. Talarico asked the firm if they intended to submit the data for the historical control group discussed at the June 6, 2000 teleconference. The firm responded that they had data on approximately 20 appropriate patients and could submit it by the end of this month. They asked if the Division could commit to reviewing the data before the August 6, 2000 12-month user fee due date. Dr. Talarico explained that the Division would do its best to review the data as expeditiously as possible, but could not commit to a specific date. She added that, although it may be necessary to take a 3-month extension on the August 6 due date, the action will be taken as soon as possible.

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NDA 21-135

Page 3

The call was then concluded.

/S/  
Brian Strongin  
Regulatory Health Project Manager

~~6/12/00~~ 6/12/00

cc: Original NDA 21-135  
HFD-180/Div. File  
HFD-180/Brian Strongin  
HFD-180/M.Lu  
HFD-180/K.Robie-Suh

TELECON

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ON ORIGINAL



S. D. G. n

## MEMORANDUM OF TELECON

DATE: June 6, 2000

APPLICATION NUMBER: NDA 21-135; Venofer (iron sucrose injection)

BETWEEN:

Luitpold Pharmaceuticals, Inc.

Mary Jane Helenek  
Suzanne Gagnon, M.D.  
Lilliam Kingsbury, Ph.D.

Peter S. Reichertz

Ted Smith, Ph.D.

Senior Vice President  
Vice President of Clinical Research and Development  
Senior Vice-President, Global Data Division  
Phoenix Life Sciences (CRO)  
Counsel to Luitpold, Arent Fox Kintner Plotkin & Kahn,  
PLLC  
Vice President of Technical Operations, Auxillium A<sup>2</sup>

AND

The Division of Gastrointestinal and Coagulation Drug Products

Lilia Talarico, M.D.  
Kathy Robie-Suh, M.D., Ph.D.  
Min Lu, M.D.  
Tom Permutt, Ph.D.  
Mushfiqur Rashid, Ph.D.  
Brian Strongin

Director  
Medical Team Leader, Hematology  
Medical Officer  
Team Leader, Biometrics  
Mathematical Statistician  
Regulatory Health Project Manager

SUBJECT: Clinical and Statistical Comments

### Background

NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. Dialysis-associated iron deficiency anemia;

February 1, 2000 the firm submitted a protocol entitled, "An Open Label Study of the Safety of Venofer [Iron Sucrose Injection] When Administered Without a Test Dose" to IND — also



for Venofer®. Comments and recommendations regarding the protocol were sent to the firm in an information request letter dated March 29, 2000. In an April 27, 2000 teleconference with the firm, the Division discussed the comments/recommendations regarding the protocol as well as provided comments regarding the efficacy database for NDA 21-135. (See Medical Officer's Review dated May 1, 2000, IND — for a record of the discussion.) The firm requested today's call to follow-up the previous discussion.

### Today's Call

Dr. Permutt asked the firm to describe Figure 1 in their June 6, 2000 submission to NDA 21-135. They described it as a graph of the 95% confidence intervals for the change in mean hemoglobin values between the screening and baseline measurements and between the baseline and end of treatment measurements for the van-Zyl Smit Study, and for Studies LU98001 and LU98002 (the pivotal studies supporting efficacy in NDA 21-135). Dr. Permutt commented that the figure seemed to indicate that there was little systematic change between the screening and baseline measurements. Referring to the scatterplot graph of change in hemoglobin values from screening to baseline and from baseline to end of treatment for Study LU98001 in their June 6, 2000 submission to NDA 21-135, the firm noted that most patients were clustered around a 1 gm/dl increase in hemoglobin and the increase in hemoglobin between baseline and end of treatment was greater than that between screening and baseline for most patients. In response to Dr. Permutt's question, the firm stated that they had not calculated a correlation between the screening and baseline values.

Dr. Permutt commented that baseline controlled studies are fundamentally problematic, which is a reason this study design is not often used. Baseline controlled studies are best when the baseline period is very stable and the treatment effect is very large. He added that although there is some indication that the effect during the treatment period was larger than that seen between the baseline and screening values, the Division still had concerns. Dr. Robie-Suh added that it was critical that the data demonstrate that the patients were stable between the screening and baseline values and that their anemia was not influenced during that period by other factors. She explained that often patients only had one or two measurements for hemoglobin during that period and that a run-in period with several measurements would have been preferable in this case. Patients may have improved due to epoetin, better compliance with treatment and other factors. It is difficult for the Division to tease out the effect of iron from the effect of other factors such as epoetin, blood loss, compliance etc. The modest clinical benefit makes the variability during the baseline period a more critical problem in the efficacy assessment. Dr. Talarico added that in a baseline-controlled study it is critical to demonstrate that the patients had a stable baseline. She added that often patients improved nearly as much during the baseline period as during the treatment period.

Dr. Talarico explained that more, stronger data is needed to support the existing data. She had the following suggestions:



1. Perform another clinical trial, preferably of parallel, placebo-controlled or active controlled design.
2. Develop a historical control group to use for comparison with efficacy data you have generated.
3. Perform another baseline controlled study using dialysis patients unresponsive to oral iron. Patients must have a very well documented baseline demonstrated to be stable. A run-in period where several values of the endpoints are measured is necessary. It is important to have small variability both between and among patients.

The firm stated that they may be able to develop a historical control group for comparison to the efficacy data from their pivotal studies. Dr. Talarico responded that this would be acceptable, but that the firm must demonstrate comparability between the treatment and historical control populations and that the patients cannot be a selected subpopulation. Dr. Permutt added that the similarity of the patient populations would be a review issue. Dr. Robie-Suh cautioned the firm that if the historical control group receives epoetin, the effects from epoetin must be separated from the effects of iron.

Drs. Permutt and Robie-Suh summarized the Division's recommendations by explaining that the firm has not provided enough data to adequately support the existence of a stable baseline period. The general view of historically controlled and baseline controlled studies is that they are appropriate where a concurrent control is not possible and a large treatment effect is seen. They added that concurrent controlled studies may be possible in this case and are preferred. However, a historical control may be acceptable.

The call was then concluded.

/S/

6/9/00

Brian Strongin  
Regulatory Health Project Manager

cc: Original NDA 21-135  
HFD-180/Div. File  
HFD-180/Brian Strongin  
HFD-180/M.Lu  
HFD-180/K.Robie-Suh

TELECON

APPEARS THIS WAY  
ON ORIGINAL



## MEMORANDUM OF TELECON

DATE: February 25, 2000

APPLICATION NUMBER: NDA 21-135; Venofer (iron sucrose injection)

BETWEEN:

Name: Peter Reichertz, Esq.; Arent Fox  
Phone: (202) 857-6378  
Representing: Luitpold Pharmaceuticals

AND

Name: Brian Strongin, Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: DSI Audit of Gasché Crohn's Disease Study and Chemical Classification Code

### Background

NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. dialysis-associated iron deficiency anemia;

Efficacy in dialysis-associated anemia is supported by two pivotal studies. Study VENO/BGSA-VIFOR/001 FARMOVS 52/93 is a multi-center, baseline-controlled study conducted in 132 patients in South Africa (van Zyl-Smit et al, 1997). Study LU98002 is a multicenter study in 23 patients designed primarily to determine whether Venofer® can be safely used in patients with dialysis-associated anemia who had previously demonstrated anaphylactic reactions to iron dextran, although efficacy endpoints were also measured. Efficacy for the remaining indications is supported by 27 publications/study reports (7 controlled, 3 with data tabulations).

On October 7, 1999 the Division requested clinical inspections by the Division of Scientific Investigations for several study sites including a site for Crohn's Disease patients and a site for ulcerative colitis patients in the study entitled, "Iron deficiency anemia unresponsive to oral iron" conducted by Dr. Christoph Gasché at Vienna University Hospital, Austria. These studies were classified by the firm as an "ulcerative colitis" study and a "Crohn's Disease" study. On February 2, 2000, the firm submitted a letter to their application describing the "Crohn's Disease" study as not being capable of, "...withstand(ing) an audit and therefore not a proper use



NDA 21-135

Page 2 of 2

of Dr. Malek's time."

**Today's Call**

Mr. Reichertz expressed the firm's concern that the DSI audit of the "ulcerative colitis" study had been canceled. I explained that the audit had been delayed until after the Division received the results of the audit of the van Zyl-Smit study and had not been canceled. The delay was due to resource limitations.

In response to Mr. Reichertz' question, I explained that if the firm is planning to request designation of a particular chemical classification code for their application, they should submit arguments with all necessary supporting data and information as soon as possible. A decision must be made before approval.

The call was then concluded.

/S/

2/25/00

Brian Strongin  
Regulatory Health Project Manager

cc: Original NDA 21-135  
HFD-180/Div. File  
HFD-180/Brian Strongin  
HFD-180/K.Robie-Suh  
HFD-180/M.Lu  
HFD-180/L.Zhou  
HFD-180/R.Frankewich

TELECON

APPEARS THIS WAY -  
ON ORIGINAL



## MEMORANDUM OF TELECON

DATE: February 14, 2000

APPLICATION NUMBER: NDA 21-135; Venofer (iron sucrose injection)

BETWEEN:

Name: Peter Reichertz, Esq.; Arent Fox

Phone: (202) 857-6378

Representing: Luitpold Pharmaceuticals

AND

Name: Brian Strongin, Regulatory Health Project Manager

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Statistical Information Requests

### Background

NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. dialysis-associated iron deficiency anemia;

Efficacy in dialysis-associated anemia is supported by three pivotal studies. Study VENO/BGSA-VIFOR/001 FARMOVS 52/93 is a multi-center, baseline-controlled study conducted in 132 patients in South Africa (van Zyl-Smit et al, 1997). Study LU98002 is a multicenter study in 23 patients designed primarily to determine whether Venofer® can be safely used in patients with dialysis-associated anemia who had previously demonstrated anaphylactic reactions to iron dextran, although efficacy endpoints were also measured. Study LU98001 is a multi-center, baseline-controlled study conducted in 77 hemodialysis patients in the United States. Efficacy for the remaining indications is supported by 27 publications/study reports (7 controlled, 3 with data tabulations).

### Today's Call

The following information requests were made:



NDA 21-135

Page 2

Please submit the following for Study LU98001:

1. Efficacy data in SAS data set format;
2. A description of the variables in the SAS data sets;
3. SAS programs; and
4. Subgroup analyses (age, sex, race, etc.) if not previously submitted.

Submit this information following the Guidance for Industry entitled, "Providing Regulatory Submissions in Electronic Format – General Considerations" on the CDER website.

The call was then concluded.

/S/

2/14/00

Brian Strongin  
Regulatory Health Project Manager

cc: Original NDA 21-135  
HFD-180/Div. File  
HFD-180/Brian Strongin  
HFD-180/M.Rashid

TELECON

APPEARS THIS WAY  
ON ORIGINAL



# MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 10, 2000

FROM: Brian Strongin, Regulatory Health Project Manager 151 2-14-00  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Kathy Robie-Suh, M.D., Ph.D. Team Leader, Hematology; HFD-180  
Lilia Talarico, M.D. Director, HFD-180 151 2-14-00

SUBJECT: NDA 21-135, Venofer (iron sucrose injection); Justification for 505(b)(1)  
Classification

TO: Wayne Mitchell, Regulatory Policy Staff

## Background

NDA 21-135 for Venofer (iron sucrose injection) was submitted by Luitpold Pharmaceuticals August 6, 1999. It provides for the following indications: (1) treatment of dialysis-associated anemia;

Efficacy in dialysis-associated anemia is supported by three pivotal studies. Study VENO/BGSA-VIFOR/001 FARMOVS 52/93 is a multi-center, baseline-controlled study conducted in 132 patients in South Africa (van Zyl-Smit et al, 1997). Study LU98002 is a multicenter, baseline-controlled study conducted in 23 patients designed primarily to determine whether Venofer® can be safely used in patients with dialysis-associated anemia who had previously demonstrated anaphylactic reactions to iron dextran, although efficacy endpoints were also measured. Study LU98001 is a multi-center, baseline-controlled study conducted in 77 hemodialysis patients in the United States. Efficacy for the remaining indications is supported by 27 publications/study reports (7 controlled, 3 with data tabulations).

This application was filed October 5, 1999 as a 505(b)(1) application and is now pending.

## Justification for the 505(b)(1) Classification



1. Preclinical Pharmacology/Toxicology Studies

NDA 21-135 includes a full range of preclinical studies. The greatest number of studies and the most critical studies were performed at \_\_\_\_\_ for Luitpold Pharmaceuticals and included all data necessary to perform a complete review. These studies are supported by published data that are not essential for approval (See Attachment One).

2. Clinical Studies

A. All clinical studies were performed either by or for the sponsor, Luitpold Pharmaceuticals. Complete study reports including protocols, data tabulations, case report forms, and other data necessary to perform a complete review were submitted for all pivotal studies (see Attachment Two).

B. All pivotal studies in support of the treatment of dialysis associated anemia involved a baseline control, a form of historical control.

Use of an historical control is allowed under 21 CFR 314.126(b)(2)(v). The draft ICH E10 document (Federal Register, 64(185): 51767-51780; September 24, 1999) elaborates further under Section 1.3.5 *External Control (Including Historical Control)*: "Baseline-controlled studies, in which subjects' status on therapy is compared with status before therapy (e.g., blood pressure, tumor size), are a variation of this type of control. In this case, the changes from baseline are often compared to a general impression of what would have happened without intervention, rather than to a specific historical experience, although a more defined experience can also be used."

Interpretation of historically controlled studies is frequently problematic because historical control populations usually cannot be assessed as well with regard to important variables as can concurrent control populations. As such, they are likely to be more subject to bias. For example: control subjects (subjects prior to starting study treatment) will not have had the positive psychological advantages of knowing they were participating in a clinical trial; subjects may become more compliant with their overall treatment plan as well as acquire additional ancillary therapeutic care upon entry into a trial, and collection of data for the historical control population may not be as complete as for the population when on study treatment.

Historical controls may potentially be useful when a number of criteria are met including, but not limited to, the following: the natural history including course and outcome of the disease are well-known, the course of the disease is such that it is not changing significantly over the time of the study, the treatment of patients



prior to the study is precisely defined, there are no significant changes in the diagnosis or management of the patients from the time of the historical data collection through the study period, and the magnitude of the treatment effect expected is large. . When a historical control is used, it is part of the task of the sponsor in presenting the NDA application to make the case for adequacy of the historical control used in the studies submitted and this issue is dealt with in the review of the application.

- C. Pivotal studies in support of the treatment of anemia of other causes involved either baseline control, active control, or placebo control.

**ATTACHMENTS**

cc:

NDA 21-135

HFD-180/Div.File

HFD-180/K.Robie-Suh

HFD-180/D.Joseph

HFD-180/J.Choudary

Drafted by: BKS/February 11, 2000

R/d init: LT/February 14, 2000

Final: BKS/February 14, 2000

Filename: \_\_\_\_\_

**MEMORANDUM**

**APPEARS THIS WAY  
ON ORIGINAL**



ATTACHMENT ONE

PRECLINICAL STUDIES AND TESTING LABORATORIES:

Type of Study and Laboratory	Study/Report #	Drug Lot #.	Page #
Pharmacology:			5
ADME:			
Absorption in Rats Vifor (International) Inc., Switzerland	SR-1005/E01	559209A2	7
Distribution in Rats Vifor (International) Inc., Switzerland	SR-1005/E01	559209A2	8
Distribution in Rats <sup>1</sup> Vifor (International) Inc., Switzerland	SR-1020/E01	572109	10
Distribution in Minipigs <sup>1</sup> _____, _____	---	---	11
Distribution in Rats <sup>1</sup> Kreuzer and Kirchgessner, J Anim Physiol Anim Nutr, 65, 1991	---	---	12
Cellular Distribution in Rats Gamerding and Pietzonka, Zeitschrift für die Gesamte Experimentelle Medizin Bd, 128s: 148-157, 1956.	---	---	13
Distribution in Pregnant Rabbits and Fetuses Pribilla, Acta Haematologica, 12(6), 372, 1954.			14
Excretion in Rats Vifor (International) Inc., Switzerland	SR-1005/E01	559209A2	16
Excretion in Rats and Transfer to Offspring <sup>1</sup> Vifor (International) Inc., Switzerland	SR-1020/E01	572109	17
Toxicology:			
Acute Toxicity in Rats and Mice (i.v., s.c., p.o.) <sup>1</sup> _____	223	---	19
Acute Toxicity in Rats and Mice (i.v., s.c.) <sup>1</sup> _____	---	---	21
7-Day Intravenous Toxicity in Rats <sup>1</sup> _____	---	---	22
13-Week I.V. Infusion Toxicity in Rats with Weekly Dosing <sup>1</sup> _____	VFR 3/951491	330109A2	23
13-Week IV Infusion Toxicity in Rats with 3 Doses Per Week _____	LPL 001/992101	807119	26
10-Week Intravenous Toxicity Study in Dogs Brown et al., J-Lab Clin Med, 50(6), 362, 1957.	---	---	33



13-Week I.V. Infusion Toxicity in Dogs with Weekly Dosing <sup>1</sup>	VFR 5/951735	330109A2	33
13-Week I.V. Infusion Toxicity in Dogs with 3 Doses Per Week	LPL 002/992102	807119	37
<b>Reproductive Toxicology:</b>			
Segment I Fertility and Early Embryonic Study in Rats	LPL 003/992500	807119	43
Segment II Intravenous Teratogenicity Study in Rats <sup>1</sup>	VFR 16-974254	676109 692109A1	46
Segment II Intravenous Teratogenicity Study in Rabbits	VFR026/983656	711119	51
<b>Genetic Toxicology:</b>			
Bacterial Mutation Assay <sup>1</sup>	96/VFR012/1211	572109	61
Bacterial Mutation Assay <sup>1</sup>	265	---	62
Mammalian Cell Mutation Assay <sup>1</sup>	VFR 014/971264	572109	63
Mouse Micronucleus Test <sup>1</sup>	96/VFR013/1243	572109	65
Chromosome Aberration Test in Human Lymphocytes <sup>1</sup>	VFR 4/950317	330109A2	66
<b>Special Toxicology Studies:</b>			
Perivenous Tolerance in Rabbits <sup>1</sup>	VFR 2/951737	330109A2	67
Intra-arterial Tolerance in Rabbits <sup>1</sup>	VFR 1/951736	330109A2	68

<sup>1</sup> Study was reviewed in IND \_\_\_\_\_

Several studies that were included in this application were previously reviewed in IND \_\_\_\_\_. These studies include the following: distribution in rats; distribution study in minipigs; distribution study in rats using iron-polymaltose (iron dextrin); excretion and transfer to offspring in rats; acute toxicity in rats and mice with intravenous, subcutaneous, and oral administration; acute toxicity in rats and mice with intravenous and subcutaneous administration; 7-day intravenous toxicity in rats; 13-week IV infusion study in rats with weekly



## ATTACHMENT TWO

### Summary Description of Studies Having Some Supporting Documentation Provided in the NDA Submission

Report	Start Date/Location	Indication and Number of Patients	Design	Treatments	Materials Provided
<b>End Stage Renal Disease:</b>					
VENO/BGSA-VIFOR/001 FARMOVS 52/93 (van Zyl-Smit study)	8/94; 5 centers in South Africa	132 hemodialysis patients	open, single arm, 2-period (treatment and observation) with pts serving as their own controls	50mg Venofer test dose into hemodialysis venous line; then 100mg in venous line 2-3 times weekly	protocol (including copy of CRF); individual Venofer administration data; individual patient data (med hx, PE, therapy, Venofer adm, AEs); statistical analysis plan after study completion; publication
LU98002	1/99; 5 centers in U.S.	23 hemodialysis patients (7 with hx of severe anaphylactoid reaction to iron dextran; 16 with hx of mild reaction)	open, single arm, 2 period study (pretreatment and observation)	100mg Venofer i.v. in dialysis line (by slow infusion of diluted drug or slow injection of undiluted drug) in each successive session for up to cumulative dose of 1000mg	protocol (including copy of CRF); investigators CVs; individual patient data listings; statistical analysis plan; For "deaths", "other serious AEs", "AE withdrawals" - sponsor indicates "not applicable"; (Reviewer note: However, probably 1 patient 00010002/MP/A, woman who developed unstable angina should be classified as AE w/d). CRFs - "not applicable"
RetroVenofer Al Mom-01	1994; Saudi Arabia	123 chronic renal failure patients (53 A, 70 B)	open, parallel group, single center, controlled	A: 100mg Venofer i.v. weekly + 50IU/kg EPO i.v. 3 times weekly for 12 wks vs. B: 50IU/kg EPO i.v. 3 times weekly for 12 weeks; EPO increased monthly in poor responders	Protocol not available; CRF copy with brief (1 page) description of study plan; CV of main investigator; data listings (SAS tables); informed consent; data entry for whether pt d/c treatment is not available for 119 pts (value "no" for 4 pts; these 4 were excluded [1 renal transplant; 3 moved to other city]); no AEs reported.
RetroVenofer Yav01	6/97; Turkey	30 hemodialysis patients (17 Group I; 13 Group II)	open, non-randomized, single center; parallel groups	Group I: 50IU/kg EPO 2-3 times weekly + 25mg test dose of Venofer followed by 100mg Venofer i.v. 3 times weekly for 1 month then Venofer adjusted to ferritin levels up to 24 weeks Group II: 50IU/kg EPO 2-3 times weekly for 24 wks	Protocol not available; CRF copy; brief study plan; informed consent not available; investigator's CV; patient data listings (SAS tables); no AEs reported; No disposition data for 29 patients.)
VEN-HUS-01	3/96; Pakistan	20 hemodialysis patients (10 Group 1, 10 Group 2)	open, single center, parallel groups	Group 1: 10mg Venofer test dose followed by 100mg Venofer i.v. twice weekly + 25IU/kg EPO twice weekly for 3 months Group 2: 200mg FeSO <sub>4</sub> p.o. 3 times daily + 25IU/kg EPO twice weekly for 3 months	No formal protocol; slide presentation study description; CRF copy; patient data listings; no AEs reported; 2 pts d/c due to abnormal lab value; 18 not d/cd.
CT 107	4/97; Germany	59 hemodialysis patients (29 Group 1; 30 Group 2)	open, single-center, randomized; parallel groups	Group 1: 250mg Venofer i.v. once monthly for 6 months. Group 2: 62.5 mg iron (Ferlecit) i.v. once weekly for 6 months	Protocol (including CRF); investigator CVs; minutes of data-review meetings; patient data listings; 4 Venofer and 1 Ferlecit withdrawn due to clinical event.
Macdougall et al - single-dose bioavailability/ PK study	4/95; U.K.	60 chronic renal failure patients (20 per group)	open, single-center, randomized, parallel groups	Group 1: 200mg iron as iron polymaltose; Group 2: 200mg iron as iron dextran Group 3: 200mg iron as iron sucrose (Venofer)	Protocol with CRF; investigator CV; No data listings



				All three groups in addition were stratified by concurrent use of EPO	
Danielson	1986 and 1989; Sweden	110 hemodialysis patients	open treatment (for 12-48 months) followed by open comparative treatment	test dose of 50mg followed by 100mg iron as Ferrum Hausmann i.v. 1-3 times weekly + usual EPO for up to 48 mos; then comparison of 20 pts with continued i.v. iron + EPO vs. 3 pts with oral FeSO <sub>4</sub> for up to 126 wks	No protocol; no informed consent doc; data listings for comparative part (23 pts); No AE column in the listings. Report states "In this study, no patient had any side-effects whatsoever, but in our total experience during 6 years where more than 15,000 ampoules have been given, 3 patients have had adverse reactions."
LU98001	12/98; U.S.	77 hemodialysis patients	open treatment, baseline control	100mg iron as Venofer i.v. for up to 10 dialysis sessions with no more than 300mg administered weekly	Study report; protocol; data sets including AEs submitted on 12/7/99 (SU/BM).
<b>Anemia from Other Causes:</b>					
Beris et al.	Switzerland	45 non-anemic patients undergoing elective surgery requiring $\geq 5$ units of autologous blood	randomized, double-blind, placebo-controlled, single center, parallel groups	<u>Group 1:</u> EPO 150IU/kg (6 doses in 2 wks) + 200mg iron as Venofer given weekly for 5 weeks <u>Group 2:</u> EPO placebo + 200mg iron as Venofer given weekly for 5 weeks	Protocol with CRF; investigator CVs; data listings submitted but not decipherable
Weisbach V.	Germany	123 adult non iron deficient patients scheduled for autologous blood donation prior to surgery	open, randomized, control without treatment	<u>Group 1:</u> 100mg Fe fumarate p.o. tid from pre-op day 35 to day 1. <u>Group 2:</u> 200mg iron as Venofer i.v. after each donation <u>Group 3:</u> No iron	protocol including CRF (in German); No data listings
Gasche et al.	? 1997; Austria	40 patients wit inflammatory bowel disease with intolerance to oral iron preparations	randomized, double-blind phase (8 wks) followed by an open phase (8 wks)	Double-blind phase: <u>Group 1:</u> 200mg iron as Venofer 2x weekly for 2 wks then weekly for 6 wks + 150IU/kg EPO 3x weekly <u>Group 2:</u> : 200mg iron as Venofer 2x weekly for 2 wks then weekly for 6 wks + EPO placebo 3x weekly  Open phase: 18 Group 1 responders (Hb increase $\geq 2$ g/dl) and 15 Group 2 responders treated with i.v. Venofer alone. Six non-responders received rx with EPO + iron.	Protocol with CRF; investigator CV; informed consent; data listings; AEs reported
Gasche	?1999; Austria	20 patients wit inflamma40 patients with inflammatory bowel disease with intolerance to oral iron preparations	open-label single arm phase (8 wks) followed by an open-label 2-arm phase (8 wks)	Phase 1: All patients received 200mg iron as Venofer 2x weekly for 2 wks then weekly for 6 wks Phase 2: Patients with partial response treated with Venofer 1x weekly; non-responders were treated with Venofer + EPO.	Protocol; investigator CV; data listings; only few AEs



Bulvik et al	?1998; Israel	121 patients with intolerance to oral iron preparations	open, single-center, 2 treatment groups (treatment up to 3 mos)	<p><u>Group A:</u> 10 infusions of 125 mg iron gluconate i.v. scheduled every 1-7 days</p> <p><u>Group B:</u> 10 infusions of 100mg iron as Venofer i.v. scheduled every 1-7 days</p>	No protocol; sample CRF; data listings (cryptic); AEs recorded as "yes/no"; some symptoms recorded
Bemiere et al	?1997; France	16 children 2-17 yrs of age having anemia post-orthopedic surgery	open, historical control (matching patient group who had been treated post-op with oral iron)	Venofer 3mg/kg/day i.v. for up to 3 mos. Control patients had received 10mg/kg/day oral ferrous fumarate in 3 divided doses for 5-6 days	No protocol; No data listings.

based on information from sponsor's tables, NDA Vol. 1.18, pp. 11 through 32, Vol. 1.36, pp. 8 through 41, Vol. 1.40, pp. 37 through 71 and information in individual study reports.

APPEARS THIS WAY  
ON ORIGINAL





DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-135

Food and Drug Administration  
Rockville MD 20857

Luitpold Pharmaceuticals, Inc.  
c/o Arent Fox Kintner Plotkin & Kahn, PLLC  
Attention: Peter S. Reichertz, Esq.  
1050 Connecticut Avenue  
Washington, D.C., 20036-6378

OCT - 7 1999

Dear Mr. Reichertz:

Please refer to your August 6, 1999 new drug application for Venofer (iron sucrose injection).

We are reviewing the chemistry, manufacturing, and controls and clinical sections of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Chemistry, Manufacturing, and Controls



Clinical

1. Provide an analysis of the safety and efficacy data by gender, race, and age for all studies for which data tabulations were submitted.
2. Provide an analysis of the safety and efficacy data by center for Study VENO/BGSA-VIFOR/001 FARMOVS 52/93 (van Zyl-Smit) and Study LU98002.
3. Clarify how many patients were enrolled in each center in Study VENO/BGSA-VIFOR/001 FARMOVS 52/93 (van Zyl-Smit).

If you have any questions, contact Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

/S/

for

Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and Coagulation Drug Products,  
(HFD-180)  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL



## MEMORANDUM OF TELECON

DATE: January 7, 2000

APPLICATION NUMBER: NDA 21-135; Venofer (iron sucrose injection)

BETWEEN:

Name: Peter Reichertz, Esq.; Arent Fox

Phone: (202) 857-6378

Representing: Luitpold Pharmaceuticals

AND

Name: Brian Strongin, Regulatory Health Project Manager

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical Information Requests

### Background

NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. dialysis-associated iron deficiency anemia;

Efficacy in dialysis-associated anemia is supported by two pivotal studies. Study VENO/BGSA-VIFOR/001 FARMOVS 52/93 is a multi-center, baseline-controlled study conducted in 132 patients in South Africa (van Zyl-Smit et al, 1997). Study LU98002 is a multicenter study in 23 patients designed primarily to determine whether Venofer® can be safely used in patients with dialysis-associated anemia who had previously demonstrated anaphylactic reactions to iron dextran, although efficacy endpoints were also measured. Efficacy for the remaining indications is supported by 27 publications/study reports (7 controlled, 3 with data tabulations).

APPEARS THIS WAY  
ON ORIGINAL



**Today's Call**

The following information requests were conveyed to the firm:

1. For the Table of Studies in the Integrated Summary of Safety (NDA Vol. 1.40), identify the brand name of iron sucrose used in each of the listed studies. Tabulate and summarize separately safety information from those studies using Venofer brand, Ferrum Hausmann brand or Ferosac brand iron sucrose.
2. For the post-marketing safety surveillance summary, tabulate and summarize separately safety information for patients using Venofer brand, Ferrum Hausmann brand or Ferosac brand iron sucrose.

The call was then concluded.

/S/

1/7/00

Brian Strongin  
Regulatory Health Project Manager

cc: Original NDA 21-135  
HFD-180/Div. File  
HFD-180/Brian Strongin  
HFD-180/K.Robie-Suh  
HFD-180/M.Lu

TELECON

APPEARS THIS WAY  
ON ORIGINAL



## MEMORANDUM OF TELECON

DATE: December 20, 1999

APPLICATION NUMBER: NDA 21-135; Venofer (iron sucrose injection)

BETWEEN:

Name: Peter Reichertz, Esq.; Arent Fox

Phone: (202) 857-6378

Representing: Luitpold Pharmaceuticals

AND

Name: Brian Strongin, Regulatory Health Project Manager

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Request for a Ninety-Day Conference

### Background

NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. dialysis-associated iron deficiency anemia;

Efficacy in dialysis-associated anemia is supported by two pivotal studies. Study VENO/BGSA-VIFOR/001 FARMOVS 52/93 is a multi-center, baseline-controlled study conducted in 132 patients in South Africa (van Zyl-Smit et al, 1997). Study LU98002 is a multicenter study in 23 patients designed primarily to determine whether Venofer® can be safely used in patients with dialysis-associated anemia who had previously demonstrated anaphylactic reactions to iron dextran, although efficacy endpoints were also measured. Efficacy for the remaining indications is supported by 27 publications/study reports (7 controlled, 3 with data tabulations).

On December 13, 1999, the applicant requested a ninety-day conference per 21 CFR 314.102(c). A copy of the meeting request is attached.

APPEARS THIS WAY

ON ORIGINAL



**Today's Call**

I provided the following responses to the firm's questions.

1. NDA 21-135 is under review. Additional information will be requested via telephone or letter when necessary.
2. Clinical site audits for some centers will be conducted. I believe that Dr. Khairy Malek of the Division of Scientific Investigations has contacted you.
3. Manufacturing site inspections will be conducted.
4. We suggest contacting the Division of Drug Marketing, Advertising, and Communications for responses to your questions regarding the marketing of Ferlecit®.

Mr. Reichertz stated that he would relay the responses to the firm and call back if necessary. The call was then concluded.

/S/

12/30/99

Brian Strongin  
Regulatory Health Project Manager

cc: Original NDA 21-135  
HFD-180/Div. File  
HFD-180/Brian Strongin  
HFD-180/K.Robie-Suh  
HFD-180/M.Lu

TELECON

APPEARS THIS WAY  
ON ORIGINAL



Arent Fox Kintner Plotkin & Kahn, PLLC

1050 Connecticut Avenue, NW Washington, DC 20036-5339

Phone 202/857-6000

Fax 202/857-6395

www.arentfox.com

**Peter S. Reichertz**

Direct 202/857-6378

reicherp@arentfox.com

December 13, 1999

**VIA FACSIMILE AND FEDERAL EXPRESS**

Lilia Talarico, M.D.

Director

Division of Gastrointestinal & Coagulation

Drug Products (HFD-180)

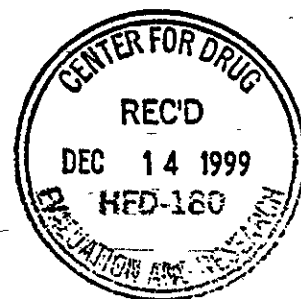
Office of Drug Evaluation III

Center for Drug Evaluation and Research

Food and Drug Administration

5600 Fishers Lane, Room 6B-24

Rockville, MD 20857



Re: REQUEST FOR 90-DAY MEETING - NDA 21-135  
VENOFER (Iron Sucrose Injection)  
Luitpold Pharmaceuticals, Inc.

Dear Dr. Talarico:

As you know, we represent Luitpold Pharmaceuticals, Inc. ("Luitpold" or "the Company"), of Shirley, New York. On behalf of our client, we hereby request the 90-day meeting under 21 C.F.R. § 314.102(c) with the appropriate Agency personnel to discuss the New Drug Application (NDA) filing for Luitpold's product VENOFER, an injection of iron sucrose intended for use in cases of iron replacement therapy.

Attached you will find a proposed agenda, including times for discussion of each agenda item, a listing of attendees, and a list of questions to be discussed at the end of the presentations, as required by MAPP 4512.1.



# Arent Fox

Lilia Talarico, M.D.

December 13, 1999

Page 2

## Purpose of the Meeting

The purpose of this meeting is to discuss:

- (1) the clinical, preclinical and other data submitted on behalf of VENOFER® by Luitpold which demonstrates that VENOFER® is safe and effective in iron replacement therapy and why prompt approval of its pending NDA is warranted;
- (2) the approval of FERRLECIT® (sodium ferric gluconate), which was approved with far less data than has been submitted by Luitpold on behalf of VENOFER®; and
- (3) what actions the Agency should take with regard to the violations by R&D Laboratories, Inc., and Schein Pharmaceutical, Inc., of agreements made with your Division, and other illegal promotional activities they have undertaken.

Luitpold expects the outcome of the meeting would be a determination that all of the available data supports the prompt approval of its pending NDA and an indication that the Agency will take action with regard to the activities of Schein Pharmaceutical, Inc.

## Immediate Approval of VENOFER® is Warranted, Given the Data on File for VENOFER® Compared to that for FERRLECIT®

As you may know per my telephone conversation of Monday, December 6, 1999, with Mr. Brian Strongin, Luitpold has now filed the study report on its LU98001 study, "A Phase II/III Open Label Study of the Safety and Efficacy of VENOFER® [Iron Sucrose Injection] in patients with Dialysis Associated Anemia", which was requested in the Pre-NDA meeting of June 9, 1998. Luitpold has now submitted three adequate and well-controlled studies in support of the use of VENOFER® in iron replacement therapy, as well as many other reports of clinical investigations of the product for that and related indications. The data submitted by Luitpold is, we believe, complete, comprehensive, accurate and convincing evidence that VENOFER® is safe and effective, and far exceeds the data in both quantity and quality of the data submitted by R&D Laboratories, Inc., in support of FERRLECIT® (sodium ferric gluconate) (NDA 20-955).



# Arent Fox

Lilia Talarico, M.D.

December 13, 1999

Page 3

Please note the following:

- (1) Segment I (Rat) Study: The NDA for FERRLECIT® was approved without this study having been submitted. It is not due until January 31, 2000, per the February 19, 1999, approval letter. This Segment I study of iron sucrose was submitted to FDA on September 22, 1999, in support of VENOFER®.
- (2) 13 Week Toxicity in the Dog: The NDA for FERRLECIT® was approved without this study having been submitted. It is not due until February 29, 2000, per the February 19, 1999, approval letter. This chronic toxicity study of iron sucrose was submitted to FDA on September 22, 1999, in support of VENOFER®.
- (3) Human Pharmacokinetic Study: The NDA for FERRLECIT® was approved without this study having been submitted. It is not due until October 31, 2000, per the February 19, 1999, approval letter. Such a study was submitted on August 6, 1999, in the VENOFER® NDA.

In addition, at least 4 other studies were required for FERRLECIT®, all as post approval studies. As an example, R&D Laboratories, Inc., must submit pediatric data for FERRLECIT®. This data was submitted on August 6, 1999, in the NDA for VENOFER®. Other studies of FERRLECIT® (not relevant to VENOFER®) were also required to be submitted by R&D Laboratories, Inc., but only after approval of the NDA for FERRLECIT®.

There is clearly more data already on file with the Agency in support of VENOFER®'s safety and effectiveness, than exists for FERRLECIT®, which is approved. Luitpold believes that prompt approval of its pending NDA for VENOFER® is warranted, not only

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# Arent Fox

Lilia Talarico, M.D.

December 13, 1999

Page 4

based on the quantity and quality of its submission, but to afford it equal treatment to that provided the approval of FERRLECIT®, and, before that, INFED® (Iron Dextran Injection).<sup>1/</sup>

## Concerns About Marketing of FERRLECIT®

We have written to you (or copied you on correspondence to DDMAC) expressing Luitpold's concerns about how FERRLECIT® is being marketed by Schein Pharmaceutical, Inc., in violation of agreements made with your Division in September 1998. It is not only misrepresenting what their product is (in an attempt to confuse people into believing it is iron sucrose), but is marketing the product as safer than iron dextran and for use as an I.V. push (which is not permitted in the labeling for the product), and for unapproved indications, such as for cancer patients. Luitpold is extremely concerned that the Agency has done nothing about these actions, especially while its NDA - which is more complete and more convincing - remains pending at the Agency.

\* \* \* \* \*

In addition to obtaining the feedback on the pending NDA to which it is entitled under 21 C.F.R. § 314.102(c), Luitpold would like to discuss at this meeting what actions the Agency will undertake with regard to the activities of Schein Pharmaceutical, Inc., and to request prompt approval of VENOFER®.

We would like to request that a slide projector, an overhead projector and a screen be available for use at the meeting.

Lastly, we would prefer that the meeting begin at anytime beginning at 10:00 a.m. on any day during the week of January 18-21, 2000.

---

<sup>1/</sup> As you may know, Schein Pharmaceutical, Inc.'s INFED® was approved in one month without any requirement to demonstrate bioequivalence to IMFERON®, the then existing reference drug. Luitpold was, however, required to submit such studies, and waited over five years to get its iron dextran product DEXFERRUM® approved.



**Arent Fox**

Lilia Talarico, M.D.

December 13, 1999

Page 5

Should you require any additional data or information, please let me know.

Sincerely,



Peter S. Reichertz

Enclosure

cc (w/enc.)  
(via facsimile)

Mr. Brian Strongin

Mr. Ralf Lange

Mary Jane Helenek, R.Ph., M.S., M.B.A.

Suzanne Gagnon, M.D.

Ms. Karenlee Voltz, M.B.A., M.H.A.

Mr. Marc L. Tokars

Kathleen Joyce, Esq.

APPEARS THIS WAY  
ON ORIGINAL



Proposed Agenda for \_\_\_\_\_ or \_\_\_\_\_ with FDA  
and Representatives of Luitpold Pharmaceuticals, Inc.  
and Arent Fox  
90-Day Meeting  
NDA-21-135  
VENOFER®  
(Iron Sucrose Injection)

Attendees:

For Luitpold Pharmaceuticals, Inc.:

Ralf Lange, President

Mary Jane Helenek, R.Ph. M.S., M.B.A., Senior Vice President

Suzanne Gagnon, M.D., Vice President of Clinical R&D

Karenlee Voltz, M.B.A., M.H.A., Senior Director of Quality Assurance  
and Regulatory Affairs

Marc L. Tokars, B.A., Director of Clinical Operations

Arent Fox (Counsel to Luitpold Pharmaceuticals, Inc.):

Peter S. Reichertz, Esq.

Kathleen Joyce, Esq.

AGENDA

- I. Introductions and Opening Remarks – Ralf Lange – 3 minutes
- II. Brief Overview of Clinical Tests of Iron Sucrose Injection performed by Luitpold, including LU98001 and LU98002 studies – Suzanne Gagnon – 5 minutes
- III. Discussion of Issues Raised in 90-Day Meeting Cover Letter - Peter Reichertz/Mary Jane Helenek – 12 minutes
- IV. FDA Feedback on Pending New Drug Application - 20 minutes
- V. – Questions & Answers – 20 minutes

APPEARS THIS WAY  
ON ORIGINAL



Questions for Discussion  
at \_\_\_\_\_ or \_\_\_\_\_ Meeting  
between FDA and Representatives of  
Luitpold Pharmaceuticals, Inc.  
and Arent Fox  
90-Day Meeting  
NDA-21-135  
VENOFER®  
(Iron Sucrose Injection)

1. Approval of VENOFER®

- a. - Is approval of VENOFER® likely based on the data submitted?
- b. Is any additional information required?
- c. When can Luitpold expect approval of its NDA?

2. Preclinical Data

- a. Are there any outstanding issues with regard to the preclinical data submitted in the NDA and in Amendments 001 and 003?

3. Clinical Data

- a. Are there any issues with regard to the two pivotal studies submitted - LU98002 and the van Zyl-Smit Study?
- b. Will the Agency be conducting inspections of the clinical sites?
- c. Are there any issues with regard to the LU98001 study submitted on December 7, 1999?
- d. Are there any other issues concerning the clinical data submitted in support of the safety and effectiveness of VENOFER®.

4. CMC Data

- a. Are there any comments on the CMC data?



- b. Are there any issues with regard to the DMF submission of Vifor (International), Inc.?
- c. Will the Agency conduct Preapproval Inspections of Luitpold and Vifor?

5. FERRLECIT®

- a. What actions does FDA intend to take with regard to the violative activities of Schein Pharmaceutical, Inc. and when?
  - (i) Will the Agency take any action with regard to promotion of FERRLECIT® as safer than iron dextran in violation of the September 1998 agreement with your Division?
  - (ii) Will the Agency take any action with regard to promotion of FERRLECIT® for use as an I.V. push?
  - (iii) Will the Agency take any action with regard to promotion of FERRLECIT® as "iron sucrose"?
  - (iv) Will the Agency take any action with regard to promotion for unapproved indications, for example, use in cancer patients?
- b. Can Luitpold expect equal treatment in the Agency's review of VENOFER®, given the fact that FERRLECIT® was approved on less data?

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ON ORIGINAL



## MEMORANDUM OF TELECON

NOV 8 1999

DATE: November 8, 1999

APPLICATION NUMBER: NDA 21-135; Venofer (iron sucrose injection)

**BETWEEN:**

Name: Peter Reichertz, Esq.; Arent Fox  
Phone: (202) 857-6378  
Representing: Luitpold Pharmaceuticals

**AND**

Name: Brian Strongin, Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Information Requests

### Background

NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. dialysis-associated iron deficiency anemia;

Efficacy in dialysis-associated anemia is supported by two pivotal studies. Study YENO/BGSA-VIFOR/001 FARMOVS 52/93 is a multi-center, baseline-controlled study conducted in 132 patients in South Africa (van Zyl-Smit et al, 1997). Study LU98002 is a multicenter study in 23 patients designed primarily to determine whether Venofer® can be safely used in patients with dialysis-associated anemia who had previously demonstrated anaphylactic reactions to iron dextran, although efficacy endpoints were also measured. Efficacy for the remaining indications is supported by 27 publications/study reports (7 controlled, 3 with data tabulations).

### Today's Call

The following information requests were made:

1. Regarding Study Retro Venofer AlMom-01 for iron deficiency anemia in hemodialysis patients and the study conducted by Dr. Christoph Gasché in ulcerative colitis patients to investigate iron deficiency anemia in patients unresponsive to oral iron, please clarify



NDA 21-135

Page 2 of 2

- if there were any deaths or withdrawals due to adverse events. If so, please submit the case report forms for these patients.
2. Regarding the study conducted by Bulvik, et al, in patients with iron deficiency anemia unresponsive to oral iron, please submit the case report forms for the patients that withdrew from the study due to adverse events.

The firm stated they would provide these. The call was then concluded.

/S/  
Brian Strongin  
Regulatory Health Project Manager

11/8/99

cc: Original NDA 21-135  
HFD-180/Div. File  
HFD-180/Brian Strongin  
HFD-180/K.Robie-Suh  
HFD-180/M.Lu

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ON ORIGINAL



**MEMORANDUM OF TELECON**

DATE: September 28, 1999

APPLICATION NUMBER: NDA 21-135; Venofer (iron sucrose injection)

**BETWEEN:**

Name: Peter Reichertz, Esq.; Arent Fox

Phone: (202) 857-6378

Representing: Luitpold Pharmaceuticals

**AND**

Name: Brian Strongin, Regulatory Health Project Manager

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Information Requests

**Background**

NDA 21-135 for Venofer® (iron sucrose injection) was submitted August 6, 1999 for the following indications:

1. dialysis-associated iron deficiency anemia:

Efficacy in dialysis-associated anemia is supported by two pivotal studies. Study VENO/BGSA-VIFOR/001 FARMOVS 52/93 is a multi-center, baseline-controlled study conducted in 132 patients in South Africa (van Zyl-Smit et al, 1997). Study LU98002 is a multicenter study in 23 patients designed primarily to determine whether Venofer® can be safely used in patients with dialysis-associated anemia who had previously demonstrated anaphylactic reactions to iron dextran, although efficacy endpoints were also measured. Efficacy for the remaining indications is supported by 27 publications/study reports (7 controlled, 3 with data tabulations).

**Today's Call**

The following information requests were made:

1. Please submit efficacy data in SAS data set format for all studies in which data tabulations were submitted. Submit this to the electronic document room following the Guidance for Industry entitled, "Providing Regulatory Submissions in Electronic Format



NDA-21-135

Page 2 of 2

- General Considerations" available on the CDER website.
- 2. Please submit unannotated labeling in WORD 97 on diskette. This may be submitted to the Project Manager's attention and need not be archived in the electronic document room.

The call was then concluded.

/S/

9/28/99

Brian Strongin  
Regulatory Health Project Manager

cc: Original NDA 21-135  
HFD-180/Div. File  
HFD-180/Brian Strongin  
HFD-180/M.Rashid

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**FACSIMILE TRANSMITTAL COVER SHEET**

Date: November 6, 2000

No. of Pages: ~~25~~ 29  
(Including Cover Sheet)

**URGENT - DELIVER IMMEDIATELY**

**PLEASE DELIVER TO:**

Name:	Fax Number:	Verify Number:
Mr. Brian Strongin	(301) 443-9285	(301) 827-7310

Attorney Number: 0160 Client Number: 015579-00005

Hard Copy Sent: No

Comments: **URGENT - DELIVER IMMEDIATELY**

Re: VENOFER® (Iron Sucrose Injection)  
NDA 21-135  
Amendment No. 21  
Sponsor: Luitpold Pharmaceuticals, Inc.  
**PHASE 4 COMMITMENT LETTER; SUBMISSION OF  
FINAL LABELING; AND SUBMISSION OF  
INFORMATION REGARDING THE DRUG PRODUCT  
AND ACTIVE INGREDIENT**

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**Arent Fox Kintner Plotkin & Kahn, PLLC**  
1050 Connecticut Ave., N.W., Washington, D.C. 20036-5339



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: CMB No. 0810-0338  
Expiration Date: April 30, 2000  
See CMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER  
21-135

APPLICANT INFORMATION

NAME OF APPLICANT

Luitpold Pharmaceuticals, Inc.

DATE OF SUBMISSION

November 6, 2000

TELEPHONE NO. (Include Area Code)  
(631) 924-4000

FACSIMILE (FAX) Number (Include Area Code)  
(631) 924-2517

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,  
and U.S. License number if previously issued):

One Luitpold Drive  
Shirley, New York 11967

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,  
ZIP Code, telephone & FAX number) IF APPLICABLE

Peter S. Reichertz, Esq.  
Arent Fox Kintner Plotkin & Kahn, PLLC  
1050 Connecticut Avenue, NW  
Washington, DC 20036-5339  
Ph: 202/857-6378 Fax: 202/857-6395

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Iron Sucrose Injection

PROPRIETARY NAME (trade name) IF ANY

Venofer®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

CODE NAME (if any)

DOSAGE FORM:

5 ml glass vial

STRENGTHS:

100 mg

ROUTE OF ADMINISTRATION:

Intravenous

(PROPOSED) INDICATION(S) FOR USE:

Iron Replacement Therapy

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50)

☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

☒ 805 (b) (1)

☐ 505 (b) (2)

☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION  
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION

(check one)

☐ ORIGINAL APPLICATION

☒ AMENDMENT TO A PENDING APPLICATION

☐ RESUBMISSION

☐ PRESUBMISSION

☐ ANNUAL REPORT

☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT

☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT

☒ LABELING SUPPLEMENT

☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

☒ OTHER

REASON FOR SUBMISSION Post Approval Commitments; Final Labeling Submission; Response to  
FDA Request

PROPOSED MARKETING STATUS (check one)

☒ PRESCRIPTION PRODUCT (Rx)

☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

☒ PAPER

☐ PAPER AND ELECTRONIC

☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFR), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or if not, when it will be ready.

See attachment

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND

DMF

DMF

DMF



This application contains the following items: (Check all that apply)		
	1. Index	
X	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
	3. Summary (21 CFR 314.50 (c))	
X	4. Chemistry section	
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
	16. Debarment certification (FD&C Act 306 (k)(1))	
	17. Field copy certification (21 CFR 314.50 (k) (3))	
	18. User Fee Cover Sheet (Form FDA 3397)	
X	19. OTHER (Specify) Post Approval Commitments	

#### CERTIFICATION

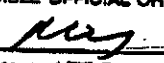
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Peter S. Reichertz, Authorized Agent	DATE November 6, 2000
ADDRESS (Street, City, State, and ZIP Code) 1050 Connecticut Avenue, NW, Washington, DC 20036-5339		Telephone Number (202 ) 857-6378

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Please DO NOT RETURN this form to this address.



November 6, 2000

**Peter S. Reichertz**  
202/857-6378  
reicherp@arentfox.com

**BY HAND**

Lilia Talarico, M.D., Director  
Division of Gastro-Intestinal and Coagulation Drug Products  
(HFD-180)  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane, Room 6B-45  
Rockville, MD 20857

Re: **VENOFER® (Iron Sucrose Injection)**  
**NDA 21-135**  
**Amendment No. 21**  
**Sponsor: Luitpold Pharmaceuticals, Inc.**  
**PHASE 4 COMMITMENT LETTER; SUBMISSION OF**  
**FINAL LABELING; AND SUBMISSION OF**  
**INFORMATION REGARDING THE DRUG PRODUCT**  
**AND ACTIVE INGREDIENT**

Dear Dr. Talarico:

This letter is written in response to your letter to me as agent for Luitpold Pharmaceuticals, Inc. (Luitpold), of November 3, 2000, and in response to our meeting dated November 2, 2000, and our telephone conferences of November 3, 2000, with regard to the above-referenced New Drug Application.

**I. PHASE 4 AND OTHER POST-APPROVAL COMMITMENTS**

In your letter of November 3, 2000, you request that Luitpold commit, in writing, to conduct the following studies or to gather the following information post-approval. You also requested a proposed schedule for the initiation and completion of these studies as well as the submission of final study reports on the requested information.

Luitpold's response to each request is as follows:



Lilia Talarico, M.D.

November 6, 2002

Page 2

1. Examine the worldwide safety database for Venofer® for occurrence of adverse events in pediatric patients by age group (neonates, infants, children, adolescents). Attempt to obtain further information on the 5 reported cases of necrotizing enterocolitis in infants, including examination of the safety database for other similar cases. No study of Venofer® in neonates and infants is requested at this time. However, you should address possible need for and risks involved with Venofer® use in very young pediatric patients;

Response: Luitpold commits to provide this information in the first annual report, as requested in the last paragraph on page 1 of your letter, and to submit the information by the due date of that report, January 6, 2002.

2. Conduct a single-dose, pharmacokinetics study of Venofer® following intravenous administration to adolescent hemodialysis patients on epoetin;

Response: Luitpold commits to conducting this study and to initiate and to complete this study within 18 months of the date of approval of the NDA, or by May 6, 2002. Luitpold commits to submit the Study Report within 6 months after completion of the study, or by November 6, 2002.

A draft protocol will be submitted for review and comment prior to initiation of the study.

3. Conduct an adequate and well-controlled clinical trial of safety and efficacy of Venofer® in the treatment of iron deficiency in children (aged 2 to 12 years) who are on hemodialysis and receive epoetin. (Use of an active control, such as oral iron, or dose ranging comparison should be considered in designing this study.);

Response: Luitpold commits to conduct this study and to initiate this study within 18 months of the date of approval, or May 6, 2002, and to complete the study within 22 months thereafter, or by March 2, 2004. Luitpold commits to submission of the Study Report within 6 months thereafter or by September 6, 2004.

Luitpold proposes to begin this study following an 18-month interim analysis of the study requested in request 4.

APPEARS THIS WAY  
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Lilia Talarico, M.D.  
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Page 3

A draft protocol will be submitted for review and comment prior to initiation of the Study.

4. Conduct a study to provide additional safety data (e.g., incidence of allergic or anaphylactic reactions, cross-reactivity with other parenteral iron preparations);

Response: Luitpold wishes to request guidance from the Division of Gastrointestinal and Coagulation Drug Products as to whether its current study - "An Open Label Study of the Safety of Venofer® [Iron Sucrose Injection] When Administered without a Test Dose", Protocol 1VEN99010 ("VEN10 Study"), which has already been submitted to the Division, would satisfy the request for this study, or, if the protocol for that study could be amended to satisfy the Division's request for the study listed above.

If the VEN10 Study as is or as amended is acceptable to satisfy this requirement, Luitpold commits to submit the Study Report within 24 months of approval, or by November 6, 2002. In this scenario, Luitpold commits to submission of the Study Report within 6 months of completion of the Study, or by May 6, 2003.

If the VEN10 study is not considered acceptable to satisfy this requirement, Luitpold commits to initiate and complete this Study within 24 months of the Agency's decision as to whether to accept the VEN10 study to satisfy this requirement, and to submit the Study Report within 6 months thereafter. Luitpold commits to submit a draft protocol for review and comment prior to initiating this Study, if the VEN10 Study protocol is not found satisfactory to meet this requirement.

5. Develop an *in vitro* release test for Venofer® and propose specifications.

Response: Luitpold commits to develop an *in vitro* release test for Venofer® (Iron Sucrose Injection) and to propose specifications therefor. Per the last sentence of the first page of your letter of November 3, 2000, Luitpold commits to submit this data (e.g., test acceptance criteria, and test data) as a prior approval supplement within 1 year of approval, or by November 6, 2001. (Please note per my telephone conversation with Mr. Brian Strongin of November 3, 2000, I understand the reference to item #4 in this sentence should have been to item #5).

## **II. FINAL LABELING**

Attached as Exhibit A is the final labeling we agreed to in our telephone conversations of November 3, 2000.



Lilia Talarico, M.D.

November 6, 2000

Page 4

Please note three minor corrections, which have been made on the submitted copy, as follows:

1. Change "does" to "doses" on page 7, line 293, in the "ADVERSE REACTIONS" section.
2. Delete the underline under "elevated liver" on page 8, line 314, in the "ADVERSE REACTIONS" section.
3. Add a "[1]" after "guidelines" on page 8, line 338, in the "OVERDOSAGE" section.
4. Delete " " in the "HOW SUPPLIED" section, and add "Contains no preservatives".

Please also advise if it is necessary to repeat the sentence:

"Parenteral drug products should be inspected visually for particulate matter and discoloration, whenever the solution and container permit."

This appears in two places - just above the "HOW SUPPLIED" section on page 10, lines 402-403, as well as in the "NOTE" a few paragraphs above, on page 9, lines 391-393, in the "DOSAGE AND ADMINISTRATION" section.

Last, per our discussion, all of Table I will be corrected to change " $\gamma$ " to " $\pm$ ", see page 3, line 117, as will the text on lines 21-25 of page 3. Attached as Exhibit B is labeling with these changes which Luitpold has prepared for use.

### **III. INFORMATION REGARDING ACTIVE INGREDIENT**

Per the request of Drs. Zhou and Frankewich, enclosed are two handouts relevant to the chemical description of the drug product and active ingredient discussed at our meeting of November 3, 2000, (Exhibit C), and page 295 of the January/February 2000 Pharmacopeial Forum Volume 26, Number 1, demonstrating that "Iron Sucrose" is the established name for the active ingredient in the product (Exhibit D).

\* \* \* \*



**Arent Fox**  
ATTORNEYS AT LAW

Lilia Talarico, M.D.

November 6, 2000

Page 5

We understand this fulfills all of the requirements necessary for approval of NDA 21-135 for Venofer® (Iron Sucrose Injection) and that an approval letter will issue today. If any clarification of this letter and the commitments and information therein is required, please contact me immediately.

We wish to thank you again for your cooperation with us on this application and look forward to a fruitful dialogue as Luitpold continues the clinical development of this product.

Again, please call me immediately if there are any questions.

Sincerely,



Peter S. Reichertz

Enclosures

cc (w/enc.)(via facsimile): Mr. Brian Strongin

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ON ORIGINAL



**EXHIBIT A**

**APPEARS THIS WAY  
ON ORIGINAL**



10 PAGE(S) REDACTED

Draft

Labeling



**EXHIBIT B**

**APPEARS THIS WAY  
ON ORIGINAL**



4 PAGE(S) REDACTED

Draft

Labeling



**EXHIBIT C**



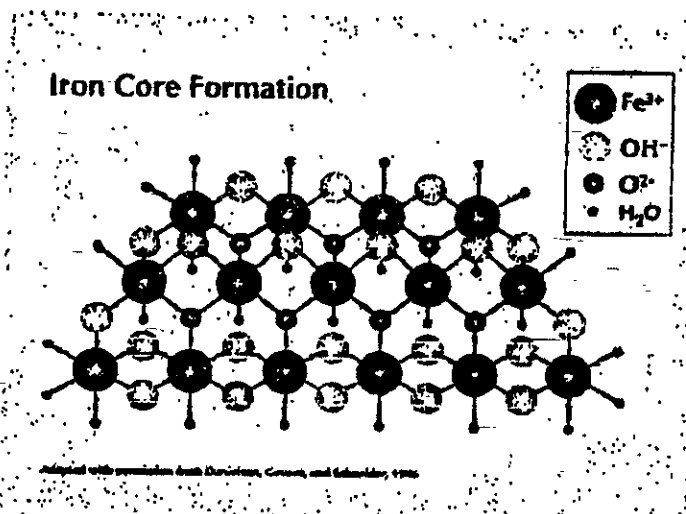
## Venofer® (Iron Sucrose Injection)

Page 1 of 2

### Structure/Composition:

Venofer® (Iron Sucrose Injection) contains as its active ingredient an iron (III) hydroxide-sucrose complex which is composed of poly-nuclear iron(III)-hydroxide cores with the following structure:

Figure 1



These iron cores are prepared by the neutralization of ferric chloride with an alkali to a pH of 2. At this pH, the saturation of hydroxide ions induces the formation of poly-nuclear iron cores, which after formation are complexed *in situ* with a suitable carbohydrate, such as sucrose. The structure of the iron core is classic coordination chemistry. The complexation of the iron core with the carbohydrate is that the OH groups on the carbohydrate replace the water molecules bonded to the iron core's outer surface.

The bonding between the iron core and the carbohydrate is a non-covalent intermolecular force, such as the attraction of partial positive charges of the core's surface iron atoms to the negative dipole moments of the carbohydrate's OH groups.

The iron(III)-hydroxide sucrose complex has a molecular weight ( $M_w$ ) of 34,000 - 60,000 daltons and a structural formula as follows:



where:  $n$  is the degree of iron polymerization and  $m$  is the number of sucrose molecules ( $C_{12}H_{22}O_{11}$ ) in complex with the polymerized iron  $[Na_2Fe_3O_8(OH) \cdot 3(H_2O)]_n$ .



NOV 5 2000 10:30AM ARKENT FOX 004 NO. 1600 P. 27/29

**Venofer® (Iron Sucrose Injection)**

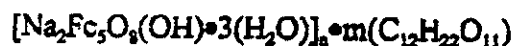
Page 2 of 2

Venofer® (Iron Sucrose Injection)'s polynuclear iron(III) hydroxide is not water soluble. It is the polynuclear iron(III) hydroxide's complexation with sucrose that renders it water soluble and suitable for injection.

We recommend that Venofer®'s package insert description be revised as follows:

**DESCRIPTION**

Venofer® (iron sucrose injection) is a brown, sterile aqueous complex of polynuclear iron(III)-hydroxide and sucrose for intravenous use. Iron sucrose has a molecular weight of approximately 34,000 – 60,000 daltons and the following proposed structural formula:



where: n is the degree of iron polymerization and m is the number of sucrose molecules in complex with the polynuclear iron(III)-hydroxide.

Venofer® is available in 5 mL single dose vials. Each 5mL contains 100 mg (20 mg/mL) of elemental as iron sucrose in water for injection. The drug product contains approximately 30% sucrose w/v (300mg/mL) and has a pH of 10.5 – 11.1. The product contains no preservatives. The osmolarity of the injection is 1250 mOsmol/L.

Therapeutic class: Hematinic

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**EXHIBIT D**

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4,4,5,5,5-Pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17 $\beta$ -diol. CAS-129453-61-8. INN; BAN. Treatment of breast cancer (antiestrogen). Faslodex (Zeneca)  $\diamond$ ICI 182,780; ZD9238

Gemifloxacin Mesylate [1998] (je mi flox' a sin).  $C_{17}H_{17}FN_3O_6S$ . 485.49. (1) (Z)-7-[3-(Aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate; (2) ( $\pm$ )-7-[3-(Aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 7-(Z)-(O-methyloxime), monomethanesulfonate. CAS-204519-65-3. Antibacterial. (LG Chemical, South Korea); (SmithKline Beecham)  $\diamond$ SB-265805-S; LB 20304a

Homosalate [1972] (hoe mee sal' ate). USP.  $C_{11}H_{12}O_3$ . 262.34. (1) Benzoic acid, 2-hydroxy-, 3,3,5-trimethylcyclohexyl ester; (2) 3,3,5-Trimethylcyclohexyl salicylate. CAS-118-56-9. INN. Sunscreen (ultraviolet light absorber). Eusolex (Rona Laboratories, Great Britain); (Wilco); Heliophan (Greiff); (Haarmann & Reimer, Germany) [Name previously used: Homomenthyl Salicylate.] USP DI Category: Ultraviolet screen.

Ibritumomab Tiuxetan [1998] (ib ri tyoo' mo mab tye ux' e tan). (1) Immunoglobulin G1, anti-human CD20 (antigen) (mouse monoclonal IDEC-Y2B8  $\gamma$ 1-chain), disulfide with mouse monoclonal IDEC-Y2B8  $\kappa$ -chain, dimer, N-[2-[bis(carboxymethyl)amino]-3-(4-isothiocyanatophenyl)propyl]-N-[2-[bis(carboxymethyl)amino]propyl]glycine conjugate; (2) Immunoglobulin G1 (mouse monoclonal IDEC-Y2B8  $\gamma$ 1-chain anti-human antigen CD20), disulfide with mouse monoclonal IDEC-Y2B8  $\kappa$ -chain, dimer, N-[2-[bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)propyl]-N-[2-[bis(carboxymethyl)amino]propyl]glycine conjugate. Molecular weight is approximately 1500 daltons. CAS-206181-63-7. Antineoplastic (monoclonal antibody). (IDEC) [Note—Yttrium-labeled ibritumomab tiuxetan is used for the treatment of non-Hodgkin's B-cell lymphoma, co-administered with rituximab.]  $\diamond$ IDEC-Y2B8; IDEC-129

Insulin Detemir [1999] (in' su lin de' te mir).  $C_{267}H_{403}N_{14}O_{71}S_6$ . 5916.90 daltons. (1) 29 $^{\circ}$ -[N $^{\circ}$ -(1-Oxotetradecyl)-L-lysine]-(1 $^{\circ}$ -21 $^{\circ}$ )-(1 $^{\circ}$ -29 $^{\circ}$ )-insulin (human); (2) 29 $^{\circ}$ -[N $^{\circ}$ -(Myristoyl)-L-lysine]-30 $^{\circ}$ -de-L-threonineinsulin (human). CAS-169148-63-4. Antidiabetic. (Novo Nordisk A/S, Denmark)  $\diamond$ NN-304

Iron Sucrose [1998] (eye' ron soo' krosee). [Saccharated Ferric Oxide is JAN.]; (1) Iron saccharate; (2) Sucrose, iron complex. CAS-8047-67-4. BAN. Treatment of iron deficiency anemia and related indications (hematinic). Venofer (Vifor, Switzerland); (Luitpold) [Names previously used: Iron Sugar, Iron Sucrose Complex, Iron Oxide Saccharated, Iron(III) hydroxide Sucrose Complex, Saccharated Iron, Saccharated Iron Oxide, Ferric Hydroxide Sucrose Complex, and Iron Saccharate.]  $\diamond$ XI-921

Izonsteride [1998] (eye zon' ster ide).  $C_{11}H_{12}N_2OS_2$ . 422.62. (1) Benzo[quinolin-3-(2H)-one, 8-[(4-ethyl-2-benzothiazolyl)thio]-1,4,4a,5,6,10b-hexahydro-4,10b-dimethyl-, (4aR-trans); (2) (4aR,10bR)-8-[(4-Ethyl-2-benzothiazolyl)thio]-1,4,4a,5,6,10b-hexahydro-4,10b-dimethylbenzo[quinolin-3-(2H)-one. CAS-176975-26-1. Treatment of prostate cancer (inhibits human type I and II isoforms of 5 $\alpha$ -reductase). (Lilly)  $\diamond$ LY320236

Lasoflofen Tartrate [1999] (la soe flox' i teen).  $C_{21}H_{21}NO_7$ ,  $C_4H_4O_6$ . 563.65. (1) 2-Naphthalenol, 5,6,7,8-tetrahydro-6-phenyl-5-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-, cis-(-)-, [5-(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1) (salt); (2) (-)-cis-5,6,7,8-Tetrahydro-6-phenyl-5-[p-[2-(1-pyrrolidinyl)ethoxy]phenyl]-2-naphthol D-tartrate (1:1) (salt). CAS-190791-29-8. Treatment and prevention of osteoporosis and breast cancer; reduction of cardiovascular risk (tissue selective estrogen-agonist/antagonist). (Pfizer)  $\diamond$ CP-336,156-CB

Lefunomide [1998] (le floo' noh mide).  $C_{12}H_{11}F_3N_3O_2$ . 270.21. (1) 4-Isoxazolecarboxamide, 5-methyl-N-[4-(trifluoromethyl)phenyl]-; (2)  $\alpha,\alpha,\alpha$ -Trifluoro-5-methyl-4-isoxazolecarboxy-p-toluidide. CAS-75706-12-6. INN; BAN. Antineoplastic (blocks PDGF receptor function, inhibiting the growth and survival of human tumor cells when administered intravenously); used in the treatment of rheumatoid arthritis when administered orally. (Hoechst AG, Germany); (Sugen)  $\diamond$ SU101; HWA-486

Listermin [1998] (lye at' er min).  $C_{1380}H_{2210}N_{420}O_{344}S_{18}$ . 30,000 daltons. (1) N-Methionylneurotrophic factor (human glial-derived), dimer; (2) N-Methionyl human glial cell line-derived neurotrophic factor. CAS-188630-14-0. Treatment of Parkinson's disease (promotion of dopaminergic neuronal process growth). (Amgen)

Maxacalcitol [1998] (max a kal' si tol).  $C_{28}H_{40}O_4$ . 418.61. (1) [1S-[1 $\alpha$ (R\*),3 $\alpha$ ,4E(1S\*,3R\*,5Z),7 $\alpha$ ]]-4-Methylene-5-[2-[octahydro-1-[1-(3-hydroxy-3-methylbutoxy)ethyl]-7a-methyl-4H-inden-4-ylidene]ethylidene-1,3-cyclohexanediol; (2) (+)-(5Z,7E,20S)-20-(3-Hydroxy-3-methylbutoxy)-9,10-secopregna-5,7,10(19)-triene-1 $\alpha$ ,3 $\beta$ -diol. CAS-103909-75-7. INN. Antipsoriatic (vitamin D analogue which inhibits proliferation of cultured keratinocytes and induces terminal differentiation). Prezios (Chugai Pharmaceutical Co., Ltd., Japan) [Names previously used: 22-Oxacalcitriol and 1 $\alpha$ ,25-Dihydroxy-22-oxavitamin D $_3$ .]  $\diamond$ OCT; SCH 209579

Mequinol [1999] (me' kwi nole).  $C_7H_6O_2$ . 124.14. (1) Phenol, 4-methoxy-; (2) p-Methoxyphenol. CAS-150-76-5. INN; DCF. Treatment of hyperpigmentation. (Nycomed) [Names previously used: 4-Methoxyphenol, 4-Hydroxyanisole, HQME; Hydroxyquinone Methyl Ether, p-Guaiacol, Leucobasal, Leucodine B, Mechinolum, Novo-Dermoquinona, 4HA, and p-Hydroxyanisole. [Note—The International Cosmetic Ingredient (INCI) name is p-hydroxyanisole.]  $\diamond$ BMS-181158

Meradimate [1999] (mer ad' i mate).  $C_{11}H_{15}NO_2$ . 275.40. (1) Cyclohexanol, 5-methyl-2-(1-methylethyl)-, 2-amino-benzoate; (2) p-Menth-3-yl anthranilate. CAS-134-09-8. Sunscreen (ultraviolet A absorber). Neo Heliopan (H & R Florasynth) [Note—The International Cosmetic Ingredient (INCI) name for meradimate is menthyl anthranilate.]

Mitomomab [1999] (mi too' mo mab). (1) Immunoglobulin G2b, anti-(GD3 ganglioside) (mouse monoclonal  $\gamma$ 2b-chain), disulfide with mouse monoclonal  $\kappa$ -chain, dimer; (2) Immunoglobulin G2b (mouse monoclonal BEC2  $\gamma$ 2b-chain anti-GD3 ganglioside), disulfide with mouse monoclonal BEC2  $\kappa$ -chain, dimer. Molecular weight is approximately 170,000 daltons. CAS-216503-58-1. Antitumor monoclonal antibody (tumor cell expressing GD3 ganglioside). (Lonza, U.K.)  $\diamond$ BEC2

Moxonidine [1998] (mox oh' ni deen).  $C_7H_{12}ClN_2O$ . 241.68. (1) 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazo-2-yl)-6-methoxy-2-methyl-; (2) 4-Chloro-5-(2-imidazo-



**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE SENT:** December 3, 1999

**DUE DATE:**  
April 1, 2000

**OPDRA CONSULT #:** 99-052

**TO (Divisions):**

Lilia Talarico, MD  
Director, Division of Gastrointestinal and Coagulation Drug Products  
HFD-180

**PRODUCT NAME:**

Venofer (Iron Sucrose Injection) 20 mg/mL

**NDA #:** 21-135

**MANUFACTURER:**

Luitpold Pharmaceuticals, Inc.

**CASE REPORT NUMBER(S):** N/A

**SUMMARY:**

In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products HFD-180). OPDRA conducted a review of the proposed proprietary name Venofer to determine the potential for confusion with approved proprietary and generic names as well as pending names.

**OPDRA RECOMMENDATION:**

OPDRA has no objections to the use of the proprietary name Venofer.

/S/ 12/2/99  
Jerry Phillips  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3246  
Fax: (301) 480-8173

/S/ 12/2/99  
Peter Monig, MD  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

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